Pediatrics

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ORIGINAL ARTICLES

OBSERVATIONS ON STAPHYLOCOCCAL INFECTIONS TREATED WITH AUREOMYCIN

By CAROLINE A. CHANDLER, M.D., EMANUEL B. SCHOENBACH, M.D., AND MORTON S. BRYER, M.D.
Baltimore, Md.

AUREOMYCIN is an antibiotic derived from a strain of Streptomyces aureofasciens.[1] *In vitro* studies have shown that it is bacteriostatic for both gram negative and gram positive micro-organisms.[2, 3] It is readily absorbed after oral administration. Although a satisfactory method of assay has not yet been worked out, preliminary assays have demonstrated low levels of the drug in the blood serum (0.3 to 2.5 μg./ml.) and high levels in the urine (up to 320 μg./ml.).[4] In animals, pharmacologic studies have shown that the toxicity of the drug is low.[5] In man, therapeutic doses up to 60 mg./kg. per day given orally have not been associated with any toxic effects except occasional nausea and vomiting.[6, 7]

In view of the fact that, *in vitro,* aureomycin is effective against a variety of staphylococci in a range of from 0.3 to 0.6 μg./ml., it was decided to treat five infants* with staphylococcal infections who were not showing a satisfactory response to combined penicillin and sulfadiazine therapy. All five infants were born in Sinai Hospital during July and early August 1948. All of them developed their infections while in the Nursery or at home shortly after discharge. Two of the patients had breast abscesses, two had

From the Departments of Preventive Medicine and Pediatrics, The Johns Hopkins University School of Medicine, Baltimore, Md.

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* In these 5 newborn infants, the aureomycin hydrochloride used was that usually supplied for intramuscular administration, 20 mgm./vial. The drug was dissolved in ½ ounce of 10% sucrose solution immediately before administration. It was well tolerated by mouth.

cellulitis and one had staphylococcal pneumonia. The infecting organism in each instance was a hemolytic Staph. aureus. *In vitro,* this organism was found to be inhibited by aureomycin in a concentration of 0.6 μg./ml.

The sixth patient in this series was a 17 month old infant who developed staphylococcal septicemia during treatment for eczema and hypoproteinemia in the Harriet Lane Home. The infecting organism in this patient was also a hemolytic Staph. aureus. It was inhibited by aureomycin in a concentration of 0.3 μg./ml. *in vitro.*

The findings on these patients are summarized in the following case reports:

Case Reports

Case 1.—J.C., a 5 wk. old white male, was readmitted to the Pediatric Ward of Sinai Hospital, with the complaint of swelling and redness of the right arm of 1½ days' duration and irritability.

One mo. prior to this admission, the patient had been transferred from the Nursery to the Pediatric Ward of Sinai Hospital because of an abscess of the right buttock. He was treated for 2 wks. with sulfadiazine, penicillin, and incision and drainage of the abscess. The abscess was found to communicate with a pilonidal sinus. He was discharged at 3 wks. of age. While home, the infant developed a pyoderma of the scalp and back and had a yellow discharge from both eyes. Thirty-six hrs. prior to admission, the mother noticed an erythematous papule on the patient's right forearm. By the time of admission, the swelling had increased and become indurated. The child was irritable and slept little. Past history and family histories were noncontributory.

Patient was a well developed and nourished, alert infant who weighed 3.5 kg. Temperature was 38.3° C. There was a slight yellow exudate in both eyes and a pyoderma of the scalp. Left breast was slightly indurated but not inflamed. On the anterior surface of the right forearm, there was an area of erythema and induration measuring 5 x 3 cm., surmounted by a pustule. Another pustule was present on the posterior surface of the same forearm. No evidence of a pilonidal sinus remained but a scar was visible at the site.

Laboratory examinations showed Hgb. 12.5 gm./100 cc., with RBC count 3.6 million/cmm., and WBC count 15.9 thousand/cmm. with neutrophiles 74%, lymphocytes 23% and monocytes 2%. Urine analysis was negative. On admission, a hemolytic Staph. aureus, in almost pure culture, was recovered from the nose and throat. Culture of the right eye 8 days after his last admission was positive for a hemolytic Staph. aureus.

On admission, the patient was given intramuscular penicillin 1,600,000 u. and sulfadiazine 0.4 gm./day. This therapy was continued for 7 days with little apparent improvement. On the 8th day after admission, penicillin and sulfadiazine were discontinued and the patient was given aureomycin 20 mgm. every 4 hrs. The drug was well tolerated and there was no evidence of nausea, vomiting or other toxic manifestations. Within 24 hrs. after initiation of therapy with aureomycin, the pyoderma had disappeared and within 36 hrs. the eye discharge had ceased and the abscess of the forearm had resolved. Aureomycin was discontinued and the patient was discharged as completely recovered 12 days after admission. Wt. at discharge was 3.8 kg.

Case 2.—N.M., a 2 wk. old white male, was readmitted to the Pediatric Ward of Sinai Hospital with the complaint of "sores on the body for the past week."

Patient had been discharged from the Nursery of Sinai Hospital at the age of 5 days with no evidence of skin infection. Seven days prior to admission, he developed prickly heat in the cervical and inguinal folds and a small pustule, pinhead in size, at the base of the scalp. Six days before admission, therapy with intramuscular penicillin and oral sulfadiazine was instituted and hot soaks were begun locally. Under this therapy, the scalp lesion drained and cleared up but the pustular rash continued up to the time of admission. Past and family histories were noncontributory.

Patient was a well developed and nourished infant of 2 wks. who weighed 3.5 kg. Temperature was 37.2° C. In the cervical and inguinal folds and over the entire upper back, on the scalp and in the groin, numerous erythematous papules and pustules were present. Physical examination was otherwise normal.

Laboratory examinations showed Hgb. 14.0 gm./100 cc., with RBC count 4.9 million/cmm. and WBC count 30 thousand/cmm. with neutrophiles 84% and lymphocytes 16%. Urine analysis was negative. Cultures of the throat and nasopharynx were positive for a hemolytic Staph. aureus and beta hemolytic streptococci.

On admission, therapy consisting of penicillin 240,000 u./day intramuscularly and sulfadiazine 0.98 gm./day orally was begun. In spite of this therapy, the lesions on the scalp developed into small, draining abscesses from which hemolytic Staph. aureus was grown in pure culture on the 3rd hospital day. By the 5th day after admission, a large pointing furuncle had developed on the posterior aspect of the left shoulder. On this day, penicillin and sulfadiazine were discontinued and aureomycin was started in a dosage of 20 mgm. every 4 hrs. by mouth. On the following day, the lesion on the shoulder was widely incised and 1 to 2 cc. of yellow pus was obtained. Hemolytic Staph. aureus was grown from this in pure culture. The next day another ½ cc. of pus was expressed from the lesion. Following this, healing took place rapidly and convalescence was uneventful. Aureomycin was well tolerated and there was no nausea, vomiting or other untoward effects. The drug was discontinued and the patient discharged 15 days after admission. Wt. at discharge was 4.4 kg.

Case 3.—D.O., an 8 day old white female, was admitted to the Pediatric Ward of Sinai Hospital with the complaint of a skin rash of 5 days' duration and a swollen red breast of 2 days' duration.

Five days before admission, patient was noted to have a mild intertriginous pyoderma which cleared slightly with the application of alcohol locally. Two days prior to admission, swelling of the left breast developed. By the morning of admission, the breast was markedly reddened and had increased in size, but there was no discharge from the nipple. Patient took her feedings poorly. Past and family histories were noncontributory.

Patient was a well developed and nourished female infant who weighed 3.0 kg. Temperature was 37.8° C. A sharply circumscribed area of redness, swelling and induration, measuring 3 x 3 x 2 cm., involved the left breast. The area was slightly fluctuant. Moderate lymphadenopathy in the left axilla was present. Except for a few areas of healing pyoderma in the neck and groin, the other physical findings were essentially normal.

Laboratory examinations showed Hgb. 17.0 gm./100 cc. with RBC 5.8 million/cmm. and WBC 20 thousand/cmm. with neutrophiles 76% and lymphocytes 24%. Urine analysis was negative. Culture of the breast abscess, which was incised on admission, showed hemolytic Staph. aureus in pure culture.

On admission, the breast abscess was incised and drained and therapy consisting of penicillin 800,000 u./day and sulfadiazine 0.6 gm./day was instituted. The breast lesion continued to drain. Penicillin and sulfadiazine were discontinued 10 days after admission and aureomycin 20 mgm. every 4 hrs. by mouth was begun. Following this, the breast lesion healed rapidly. After 3 days, aureomycin was discontinued and the patient discharged. Skin was entirely clear and the breast was healed. Wt. at discharge was 2.9 kg. Aureomycin was well tolerated and there were no toxic drug reactions.

Case 4.—R.R., an 8 day old white male, was transferred from the Nursery to the Pediatric Ward of Sinai Hospital on Sept. 12, 1948, because of engorged, erythematous breasts.

On the morning of admission, the patient had been circumcised. That evening bleeding was noted at the site of circumcision which required suturing. At this time, it was observed that both breasts were engorged and that the nipples had erythematous margins. Since it was felt that breast abscesses were developing, the patient was transferred to the Pediatric Ward.

Patient was a well developed and nourished newborn who weighed 2.8 kg. Temperature was 36.9° C. Except for the engorged breasts and nipples with erythematous margins, physical findings were essentially normal.

No laboratory examinations were performed on this patient with the exception of culture of the pus on the 8th hospital day when the breast abscess was incised and drained. From this a hemolytic Staph. aureus was grown in pure culture.

On admission, patient was given a daily dose of penicillin 180,000 u. and sulfadiazine 0.4 gm. Swelling and redness of the left breast rapidly disappeared. Since the right breast appeared to be going on to definite abscess formation, penicillin and sulfadiazine were discontinued 3 days after admission and aureomycin 20 mgm. every 4 hrs. by mouth was begun. By the 8th hospital day the right breast abscess was completely localized so incision and drainage were performed and 1 to 2 cc. of yellow pus was obtained. The drain was removed on the 9th day and, from that time until the time of discharge 3 days later, the lesion healed rapidly. Except for mild vomiting of 1 day's duration, aureomycin was well tolerated. Wt. at discharge was 3.0 kg.

Case 5.—J.R., a white male 6 wks. of age, was admitted to Sydenham Hospital on Sept. 15, 1948, with the complaint of coughing.

Patient was born at Sinai Hospital on Aug. 11, 1948. He was discharged from the Nursery 1 wk. later as a normal newborn. At 19 days of age, he developed a cold with cough and fever up to 38.3° C. Two days later he was admitted to another hospital with the diagnosis of pneumonitis of the right lung. Blood cultures were negative but throat cultures were positive for a hemolytic Staph. aureus, beta hemolytic streptococcus and streptococcus viridans. He was treated with penicillin (100,000 u. every 4 hrs.), sulfadiazine (0.2 gm. every 4 hrs.) and finally streptomycin (50,000 u. every 4 hrs.), which was begun on the 10th hospital day. Two days prior to the patient's admission to Sydenham, the hemolytic Staph. aureus was reported to be resistant to both penicillin and streptomycin. He was transferred to Sydenham Hospital on the 18th day of his disease. The past and family histories were noncontributory.

Patient was a well developed and nourished infant who weighed 3.3 kg. Temperature was 37° C. He coughed frequently, a nonproductive cough. There were a few pustules on the buttocks and some shotty lymph nodes in the inguinal region. Examination of the lungs showed impairment of resonance

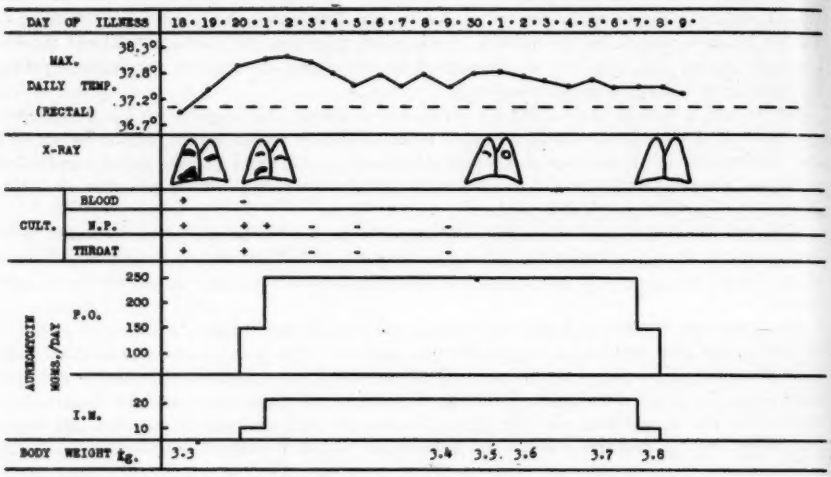

CHART I

STAPHYLOCOCCAL PNEUMONIA

J.R. Male Age 6 Wks.

over the right upper lobe and at the right base posteriorly. Breath sounds were diminished over these areas. Lungs were otherwise clear.

Laboratory examinations showed Hgb. 14.0 gm./100 cc. and WBC count of 17.4 thousand/cmm. with neutrophiles 44%, lymphocytes 52% and monocytes 4%. Urine analysis was negative. On admission, 1 blood culture was positive for Staph. albus but all subsequent blood cultures were negative. Nose and throat cultures on admission were positive for a hemolytic Staph. aureus, a few beta hemolytic streptococci and Staph. albus. Chest roentgenogram on admission was interpreted as showing pneumonia with atelectasis in the right lower lobe and an acute pneumonic process in the left lung.

On the 3rd day after admission, having received no specific therapy since admission, the patient was started on aureomycin in a dosage of 50 mgm. every 4 hrs. by mouth and 20 mgm./day by intramuscular injection. On that day, the nasopharyngeal culture was positive predominantly for the hemolytic Staph. aureus. Two days after the institution of aureomycin therapy, the nose and throat cultures became sterile and, with the exception of 5 colonies of staphylococci noted on the throat plate 6 days later, the cultures remained sterile throughout the patient's stay in the hospital. Chest roentgenogram on the 5th hospital day, 2 days after the start of aureomycin, showed considerable clearing of the lesions in the right lung with no change in the left lung. Seven days later,

chest roentgenogram showed marked clearing of the previously dense infiltration at the right base and the almost complete disappearance of the infiltration in the left lung with the exception of a single ring-like shadow. The last roentgenogram taken 19 days after admission showed the chest to be essentially clear. Clinically, the patient made a recovery during aureomycin therapy. He became afebrile within 48 hrs. and his cough disappeared over a period of 5 or 6 days. He ate and gained

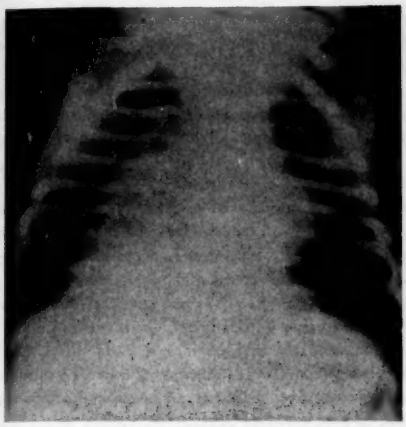

FIG. 1. Chest roentgenogram of J.R. on admission.

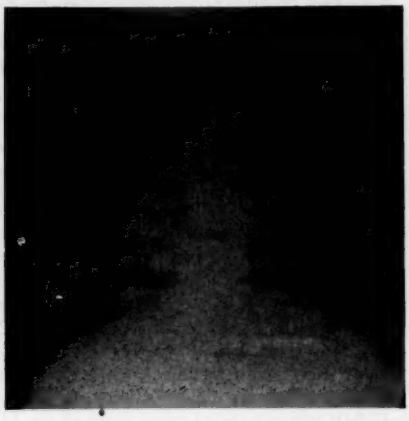

FIG. 2. Fifth day after admission.

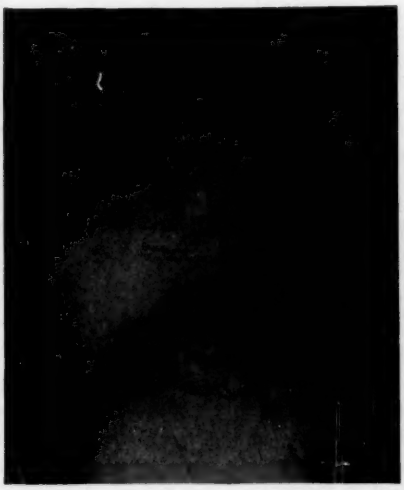

FIG. 3. Twelfth day after admission.

FIG. 4. Nineteenth day after admission.

well and, with the exception of a few loose stools on 1 or 2 days, there was no evidence of intolerance to the drug. Wt. at discharge 23 days after admission was 3.8 kg. A summary of this patient's course in the hospital is presented in Chart 1 and roentgenograms of the chest are illustrated in Figures 1 to 4.

Case 6.—A.B., a Negro male of 17 mos., was admitted to the Harriet Lane Home on Sept. 18, 1948, with the complaint of eczema and edema.

This patient developed eczema at 14 mos. of age. Six wks. and 4 wks. prior to admission, his skin became infected and he was treated for several days with penicillin and sulfadiazine. Eight days before admission, he began to have diarrhea with 4 to 5 loose stools a day. On the 5th day before admission, B. Morgani and B. Sonnei were cultured from the stools. At that time, the patient's feet and hands became swollen and he developed polydypsia. By the time he was admitted to the hospital, the edema had spread over his entire body and he had gained 1.3 kg.

Patient had a marked generalized edema with eczematous lesions on the face, neck, trunk, arms and legs. Temperature was 36° C. and he weighed 13.6 kgs. Liver edge was palpable at the costal margin. Physical examination was otherwise not remarkable.

Laboratory examinations showed Hgb. 13.5 gm./100 cc. and WBC count of 13.5 thousand/cmm. with neutrophiles 61%, lymphocytes 30% and monocytes 9%. Urine analysis was negative. Blood studies showed serum total proteins to be 3.6 mgm.% with a serum albumin of 2.4 mgm.% and globulin of 1.2 mgm.%.

Patient was treated with plasma and transfusions for low serum protein. Six days later he developed high fever, liver became enlarged to below the umbilicus, spleen became palpable and blood cultures showed a hemolytic Staph. aureus on repeated occasions. Sepsis was attributed to infection of the site where a vein had been surgically exposed to insert a continuous intravenous drip. The child was acutely ill, distended, had severe diarrhea and could not tolerate food or fluids by mouth. Penicillin up to 2 million u./day, sulfadiazine 2 to 3 gm./day, and streptomycin 200 to 1600 mgm./day were administered for 13 days without noticeable improvement. On the 16th hospital day, aureomycin therapy was begun—160 mgm. intramuscularly divided into 4 daily doses. Oral dosage was administered by stomach tube, the dose varying from 100 to 600 mgm./day. The amount absorbed orally was difficult to estimate as the dose was dissolved in water and passed through the stomach tube which was then clamped for ½ hour before constant suction was again reapplied. After 8 days, intramuscular drug was discontinued but oral medication with 300 mgm. of aureomycin a day was continued for 9 more days.

Last positive blood culture was obtained 5 days after the institution of aureomycin therapy, and subsequent blood cultures were sterile. The child improved clinically, liver returned to normal size, temperature subsided and he was able to take food and fluids by mouth. Thereafter his convalescence was uneventful except for the problem of eczema. Hypoproteinemia disappeared.

Sensitivity of the hemolytic Staph. aureus to penicillin was found to be 125 u./ml., to sulfadiazine, 0.01 gm./ml., to streptomycin, greater than 100 μg./ml. This same organism was tested on 2 occasions for aureomycin sensitivity. The strain obtained 7 days before the institution of aureomycin therapy, and that obtained after 5 days of aureomycin therapy, were both found to be inhibited by aureomycin 0.3 μg./ml.

It was the impression of those on the service that this infant, admitted with eczema and hypoproteinemia, had developed hemolytic staphylococcal septicemia with peritonitis and multiple liver abscesses and that, despite huge doses of penicillin, streptomycin and sulfonamides, he had shown no improvement until aureomycin therapy was instituted.

Discussion

The response of the first five infants to the administration of aureomycin was excellent. There was marked clinical improvement in all patients within 48 hours. This is especially noteworthy in view of the fact that prior to receiving aureomycin, all five infants had been receiving large doses of penicillin and sulfadiazine for from 3 to 15 days without obvious improvement. In patient 5, not only was there roentgen evidence of resolving pneumonia within 48 hours, but even the nose and throat cultures had become sterile within the same period of time. Only one patient required a surgical procedure after the drug was begun. In patient 4, incision and drainage of the breast abscess was performed on the fifth day of therapy, but the lesion had completely localized by that time under therapy. In this series, aureomycin was administered for a mean period of 10 days—the shortest period having been 3 days and the longest, 17. No exacerbations of fever or of infectious lesions were noted in any case after therapy had been discontinued.

Laboratory determinations of the *in vitro* susceptibility of the staphylococci isolated from the first four patients to penicillin and sulfadiazine were not performed. The organism isolated from patient 5 was reported to be resistant to penicillin and streptomycin, but the degree of resistance was not given.

The sixth patient, critically ill with septicemia, and probable peritonitis and liver abscesses, had one positive blood culture on the fifth day of aureomycin therapy, but thereafter his blood cultures remained sterile, his signs and symptoms rapidly disappeared and he made an uneventful recovery.

The optimal dose of aureomycin for bacterial infections has not yet been established, but from data now being accumulated on a variety of infections, it would appear that an excellent clinical response may be expected when daily doses of 30 to 60 mg./kg. body weight are given orally. In this series, the first five patients were given 60 mg. of drug per kg. body weight orally. Patient 5 was given an additional 20 mg. per day intramuscularly because of the severity of his infection. Patient 6 was given a total dose of 100 to 600 mg. orally and 160 intramuscularly per day. Considering the weight of the patient (13.6 kg.), the intramuscular dosage was far larger than one would ordinarily recommend.

Except for mild vomiting of one day's duration in patient 4 and a few loose stools of one to two days' duration in patient 5, aureomycin was well tolerated and there were no toxic manifestations noted in spite of the fact that five of these patients were newborn infants. This is not an isolated observation as it has been consistently true of over 90 patients of all ages[8] treated with aureomycin for other infectious diseases and of a series of five normal control subjects as well.[4] This, of course, does not rule out the possibility that toxic manifestations may appear in the future when many more patients have been treated with the drug.

Summary

Five infants with staphylococcal infections who had shown no clinical response to penicillin and sulfadiazine were successfully treated with aureomycin in the summer of 1948. Marked improvement was noted in all patients within 48 hours. The sixth patient, who was critically ill with staphylococcal septicemia and had not responded to combined penicillin, streptomycin and sulfonamide therapy, had negative blood cultures after five days of aureomycin therapy and made a rapid, uneventful recovery. No toxic effects from the drug were apparent.

Addendum

Since the completion of this manuscript, one additional infant with multiple lung abscesses has been treated successfully with aureomycin in Sinai Hospital. This patient developed his infection during the same period that the first five infants were under observation. The infecting organism in this instance was also a hemolytic Staph. aureus. After being treated for two months with penicillin, streptomycin and sulfonamides with no improvement, this patient was given aureomycin. Within one week after therapy was begun, there was clearing of the lungs by roentgen examination with beginning clinical recovery.

Acknowledgment

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Sydenham Hospital; Dr. Alexander J. Schaffer, Pediatrician in Chief, Sinai Hospital, and to members of the house staffs of these institutions for their careful observations and cooperation in this study.

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8. Personal observations.

SPANISH ABSTRACT

Observaciones sobre Infecciones Estafilocócicas Tratadas con Aureomicina

El aureomicina es un antibiótico que es bacteriostático para los organismos de unidad negativa y positiva *in vitro*. Se absorbe facilmente después de la administración oral. En el hombre las dosis terapéuticas hasta de 60 mgm./kg. al día, administradas oralmente, no han sido asociadas con efectos tóxicos, excepto nausea y vómitos de cuando en cuando.

Cinco niños contrajeron infecciones cuando estaban en la cuna de un hospital y en casa, poco tiempo después de haber sido despachados. Dos de los pacientes tenían abscesos de pecho, dos tenían celulitis y uno tenía neumonía estafilocócica. En cada caso el organismo de infección fué un aureus estafilocócico hemolítico. El sexto paciente en las series fué un infante de 17 meses de edad a quien se le desarrolló septicemia estafilocócica durante el tratamiento para eczema y para hipoproteinemia en otro hospital. El organismo de infección en este paciente fué también un aureus estafilocócico hemolítico.

Antes de recibir aureomicina los cinco primeros niños habían recibido penicilina y sulfadiazine en grandes dosis, sin haber tenido ninguna respuesta clínica. Después de la institución de la terapia de aureomicina se notó un marcado mejoramiento en todos los cinco pacientes dentro de 48 horas y después comenzó el restablecimiento completo. El sexto paciente, que estaba gravemente enfermo con septicemia estafilocócica y quien no había respondido a la terapia combinada de penicilina, estreptomicina y sulfonamide, tuvo cultivos de sangre negativos cinco días después de la terapia de aureomicina, y tuvo una mejoría rápida y sin acontecimientos. No aparecieron efectos tóxicos de la medicina.

615 North Wolfe Street

BIRTH INJURY, FOCAL EPILEPSY AND CORTICAL EXCISION

Case Report

By WILDER PENFIELD, M.D., F.R.S., AND SAMUEL LIVINGSTON, M.D.
Montreal, Canada, and Baltimore, Md.

A FOCUS within the brain which gives rise to occasional epileptic seizures may also exert an adverse influence upon general brain development and brain function. The evidence of this influence may be found in behavioral and intellectual deterioration. Excision of a discrete epileptogenic area of damaged cortex may therefore serve two purposes: to arrest the seizures and to make possible more normal development of the otherwise uninjured portions of the patient's brain. Support for this hypothesis is to be found in the following case.

H.F. had a brain injury at the time of birth. Nevertheless he seemed to develop normally up to the age of five months when he began to have seizures. From this time on there was mental deterioration until the age of 12 months when surgical removal of an epileptogenic focus was carried out. The cessation of seizures which followed operation has been associated with subsequent general improvement during the seven years which have elapsed since operation.

CASE HISTORY

H.F. was the 2nd child of healthy parents and there was no history of epilepsy or convulsions of other members of the family. Patient was born 2 wks. after the expected date by head presentation. He weighed 2.9 kg. Labor was somewhat prolonged, but the child appeared normal at the time of the delivery. However, 2 days after birth, he vomited several times and had 2 short generalized convulsions.

Physical examination at this time revealed a bulging fontanelle, but was otherwise negative. Diagnostic lumbar puncture showed that there was gross blood in the spinal fluid. During the course of the subsequent 2 days he did poorly, vomited his feedings and had 3 more short, generalized convulsions. He was given vitamin K and treated symptomatically. After the 5th day of life, he began to improve and continued to do well. He held up his head at 3 wks. of age, sat alone at 4 mos. of age, and appeared to have normal intelligence.

At the age of 5 mos., however, he had a prolonged left-sided convulsion. Following this, he began to have daily seizures consisting of stiffening of the left arm and the left leg followed by turning of the head to the left. His head would then turn to the right and he would have clonic movements in the left arm and the left leg. These convulsive episodes lasted from 5 to 30 min. and recurred daily, sometimes as often as 25 to 50 each day.

He was treated with phenobarbital, bromides and dilantin with little benefit. At the end of the 1st yr. of life, the child showed progressive mental and physical deterioration. He was unable to hold up his head or to sit alone and seemed to be completely disassociated from his surroundings. At this time, aged 1 yr., April 1941, he was admitted to the Montreal Neurological Institute.

Examination

The child neither sat up nor walked and the left arm was used less than the right. Right side

From the Montreal Neurological Institute, Department of Neurology and Neurosurgery of McGill University, Montreal, Canada, and the Department of Pediatrics of the Johns Hopkins University Medical School, Baltimore, Md.

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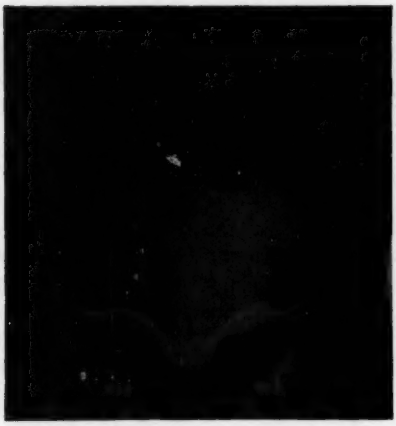

FIG. 1. Anteroposterior view of skull shows right cranial chamber to be smaller than left.

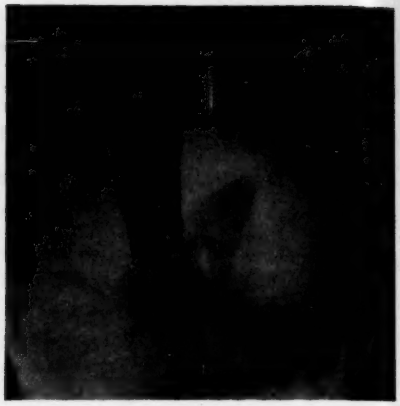

FIG. 2. Pneumoencephalogram demonstrates that anterior portions of ventricles are of about same size, but that cranial chamber on right is considerably smaller.

FIG. 3. Lateral film taken with brow up shows large superficial area of destruction over right frontal lobe.

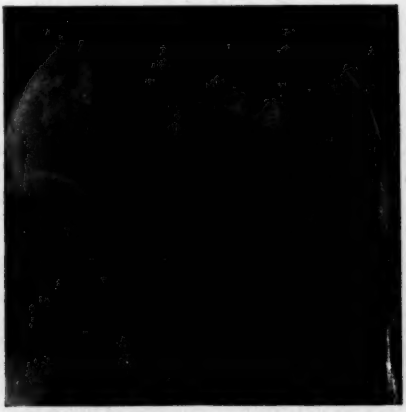

FIG. 4. Lateral film, taken with occiput up, demonstrates that oxygen has been trapped in right frontal lobe cyst; also, that posterior portions of lateral ventricles are similar in size and shape and that 4th ventricle appears normal.

of the cranium appeared to be smaller than the left. Tendon reflexes were hyperactive bilaterally. Abdominal and cremasteric reflexes were absent. Plantar response was flexor and there was no ankle clonus. Retinal examination showed a moderate degree of pallor of both discs without other evidence of abnormality. Preoperative lumbar puncture yielded normal fluid in which there were no cells. Pandy test was negative and total protein in the cerebrospinal fluid was 11 mgm./cm.

Roentgenography

Simple roentgenograms of the skull showed what was apparent from inspection of the infant's head, that the right cranial chamber was smaller than the left (Fig. 1). Asymmetry was even more obvious in the pneumoencephalogram (Fig. 2). Pneumograms demonstrated also a cyst in the right frontal region and atrophy of the right frontal lobe (Figs. 2, 3 and 4).

Preoperative Electroencephalography

Electrograms (Fig. 5) were reported as follows:

Phase reversals of spike forms, sharp waves and random delta waves occurred at standard head position C6. (This was 6½ cm. above the right external auditory meatus on the central line. It corresponded with the more posterior portion of the cyst shown by pneumography.) There was considerable spread of this electrical activity to the opposite hemisphere and to other head regions. A considerable amount of random delta occurred, especially from frontal head regions, and at times this random delta was more frequent in the left frontal region than elsewhere.

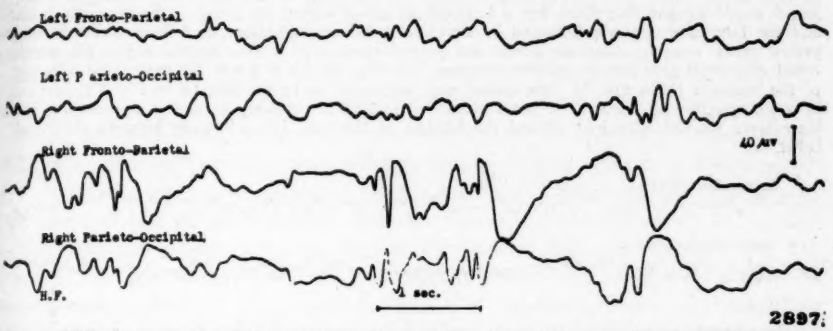

FIG. 5. EEG shows random delta and sharp waves arising from all head regions with phase reversal of spikes, sharp waves and random delta waves occurring midway between right ear and vertex.

Background rhythms were poorly organized and irregular, but this should not be considered unusual for an infant of 11½ mos. who was extremely restless.

Conclusion—There is evidence of a focal epileptogenic lesion in the right hemisphere in the vicinity of standard head position C6.

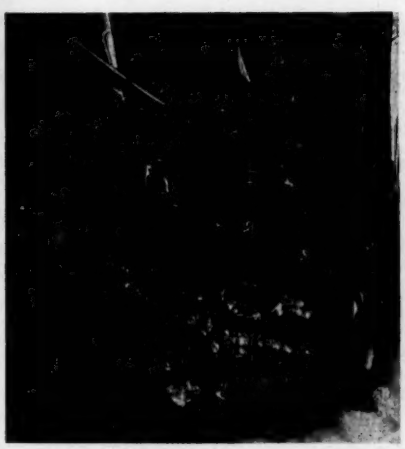

FIG. 6. Operative photograph shows right frontal lobe after dura has been opened and reflected. Cyst has been held open, which lay between right frontal lobe and falx. Cyst was result of hematoma that must have appeared at time of birth. Arrows point to yellow, atrophied epileptogenic gyri which bordered cyst.

FIG. 7. Right frontal lobe is shown as in previous figure. Marginal atrophied gyri, which were indicated in that photograph by arrows, have been removed, and also cyst wall. This leaves falx (F) exposed and ependyma (E) covering ventricle.

Operation

As a preliminary procedure, bilateral exploratory frontal trepanations were carried out. On the right side beneath the dura, there was evidence of previous bleeding but the amount of subdural hematoma remaining was not significant. Brain appeared essentially normal on the left side.

Large right-sided osteoplastic craniotomy was carried out under general anesthesia 12 days later. When the dura was opened, adhesions were found between it and the arachnoid. The operation note may be quoted verbatim:

> Placed in the midline, i.e., between frontal lobe and the falx, was a cyst (Fig. 6). This cyst might be said to be within the frontal lobe. It must include some of the previously damaged brain, and I would assume that there was a hemorrhage either within the brain, or between the brain and the falx. The cyst was bordered by a yellowish bile-stained tissue, and there was a narrow yellow gyrus, running along the lateral and posterior aspect of it (see arrows in Fig. 6), which could quite well give rise to epileptic seizures. The floor of this cyst was the ependymal covering of the ventricle (E in Fig. 7). The mesial wall was made up by the falx (F in Fig. 7), covered by a glairy-yellowish tissue. The brain elsewhere seemed to be fairly normal in appearance, but there were marked adhesions around the borders of the cyst, i.e., adhesions between dura and brain.

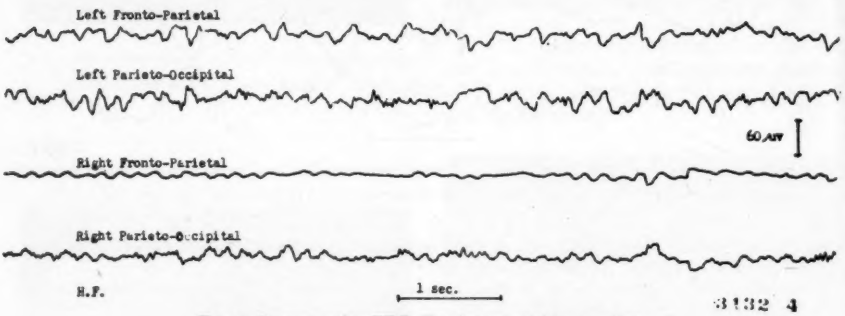

FIG. 8. Postoperative EEG. For interpretation, see text.

The narrow gyri (indicated by arrows in Fig. 6) were removed all around the cyst, leaving a fairly satisfactory bank covered with pia (Fig. 7). A gyrus had to be cut across only at 1 point. The ependymal covering of the ventricle was not opened. The dura was closed completely. The bone was replaced and fastened in place with small steel wires. The dura was drawn up to the bone, by means of silk sutures.

Operation summary—This was a birth hemorrhage which left behind it a hematoma and cavity on the medial aspect of the brain extending back as far as the motor region. It seems reasonable to assume that the mental retardation that has occurred during the 2nd 6 mos. of this child's life might be due to the unfavorable activity of the epileptogenic gyri which surrounded the cyst. Phenobarbital is to be administered following operation.

Postoperative Electroencephalography

EEG was repeated (Fig. 8) 6 wks. after the operation. This was interpreted as follows:

> The large sharp waves over the right central region, which characterized the preoperative record, are now completely absent, and a relatively quiet area exists over the right frontal lobe. There is no evidence of epileptiform discharge during this examination. There is a background rhythm at a frequency of 4-5/sec. This should be considered as low normal for a child of this age.
>
> In conclusion the electrogram suggests the successful removal of an epileptogenic focus in the right central region. There is now no indication of epileptiform activity.

Postoperative Course

At the time of discharge from the hospital in 1941, there was evidence of a considerable improvement in his general condition. He was still unable to hold up his head, but he had begun to smile and appeared much brighter than he had on admission. He had what seemed to be a few minor seizures during the 1st postoperative days. Curiously enough, these appeared only with crying. At 15 mos. of age, he was completely free of seizures and had begun to show definite improvement mentally. He held up his head well and sat alone, but made no effort to stand. He had a left-sided hemiplegia of the atonic type more marked in arm than foot. At 34 mos. of age, an evaluation of mental accomplishments placed him in the range of a 12 to 18 mo. old child. His language development was the best performance.

EEG done at 3 yrs. of age showed a 6 per second rhythm of moderately high voltage from all leads, no constant localization, but occasional spike and wave-like forms occurred in the right occipital region. Another EEG done at 6 yrs. of age revealed a pattern similar to the above.

During the course of the subsequent years, he continued to improve, both mentally and physically. A gradual reduction in the dosage of phenobarbital was started at 3 yrs. of age, and at 4 yrs. of age it was completely discontinued. He began to walk with the help of braces. At 7 yrs. of age the patient started school, and an evaluation of his intelligence at this time revealed an intelligence quotient of 62%.

Patient is now 8 yrs. of age. He has been entirely free of convulsions since about 15 mos. of age (3 mos. after the operation). He is in the second grade. A recent intelligence test reveals further improvement. He has a chronologic age of 8 yrs., 4 mos., a mental age of 6 yrs., 2 mos. and an intelligence quotient of 69%.

Discussion

When this patient was 12 mos. old, the easy conclusion would have been that the child was suffering from an unnamed degenerative cerebral disease, a disease which was producing seizures and retardation. Such a conclusion might seem to receive support from the fact that the EEG showed abnormal potentials derived from the left as well as the right hemisphere. Actually, the condition was as follows: The child had had injury to the right frontal lobe but was developing well in spite of this. He might well have grown up with no more outward evidence of the injury than a left hemiparesis had not certain partially destroyed gyri reached that stage of progressive atrophy which made them epileptogenic.

From that time on both hemispheres were at the mercy, one might say, of neuronal discharges originating in the atrophied gyri, gyri which were quite incapable of normal function themselves.

That this was the case would seem to be proved by the fact that the surgical procedure when the child was 12 months old accomplished nothing more than the removal of narrow, tough gyri which bordered a fluid-filled space adjacent to and within the right frontal lobe. The fluid in this space was not producing pressure, for it communicated with the subarachnoid channels and filled readily with oxygen which was injected intrathecally in the lumbar region. Furthermore, the right cranial chamber was smaller, not larger, than the left, indicating that there had been no more than temporary increase of pressure in the right cranial half during the first year of life.

The simple excision of these half-destroyed gyri resulted then in cessation of seizures. It terminated the deterioration of the infant and permitted resumption of more or less normal development. Similar results have been encountered after operations upon adults.* Hebb and Penfield[1] (1940) made a careful psychologic study of a man 27 years of age before and after operative removal of frontal epileptogenic scars, together with adjacent cortex, and concluded that there resulted striking postoperative improvement in personality and intellectual capacity.

The results of surgical excision of epileptic foci in a series of 200 cases have been reported by Penfield and Steelman[2] (1947).† This report concerned itself with the therapeutic effect upon the epileptic seizures. But it was a common observation that when the correct excision had been made, and even though it often included normal cerebral tissue, there frequently resulted improvement in memory, intellectual capacity and behavior.

* It has been pointed out by Jasper that focal discharging lesions produce much more generalized electrographic abnormality in infants and children than such lesions do in adults.

† In this series, there were 17 cases in which the cause was shown to be birth injury of some sort, although the age of onset of seizures varied from 1 to 20 yrs. and averaged 5 yrs. In this group, operation was followed by cessation of seizures in 76%.

It may be a matter of debate as to how important the psychologic effect of freedom from seizures may be. In an adult, this doubtless has a general beneficial effect. But certainly it is not a factor in the case of infants. One may conclude, therefore, that the seizures themselves have a deleterious effect upon the brain due to some postictal circulatory or metabolic influence. This is obviously true in some cases and less important in others.

But there is also reason to believe that an epileptic focus, if continuously active, may interfere with the function of other parts of the brain during the long periods between overt seizures. In the case of H.F., reported here, there was continuous electroencephalographic evidence of rapidly recurring discharges of high potential and short duration.

The study of this case, which has been followed closely over a period of years, together with that of other less carefully followed children, suggests that deterioration both intellectual and behavioral may sometimes result from the generalized influence of a comparatively small epileptogenic focus. Birth hemorrhage, or birth trauma, or birth ischaemia may produce a local cerebral lesion which is relatively unimportant until it ripens into the epileptogenic state. This ripening process may require 6 months, 2 years, 10 years, or even 20 years. But when the time arrives it is well to consider the possibility of the wide-spread cerebral effect of the focus as well as the inconvenience of the seizure themselves.

Summary

This eight year old boy had a cerebral hemorrhage at birth. In spite of this, however, he held up his head at three weeks, sat alone at four months and mental development seemed to be normal until he reached six months of age. Recurring cerebral seizures began at five months and soon thereafter there was marked deterioration. At 12 months, when he was operated upon, he could not hold up his head and was completely apathetic. Thereafter, seizures stopped and improvement, both mental and physical, followed.

Acknowledgment

The authors wish to acknowledge their indebtedness to Dr. Winthrop Phelps for his assistance in handling this patient and to Dr. Herbert Jasper for his study of the EEG.

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Spanish Abstract

Lesión de Nacimiento, Epilepsia Focal y Excisión Cortical: Detalle de un Caso

Un varón de 8 años de edad tuvo una hemorragia cerebral al nacer. A pesar de esto, sin embargo, levantó la cabeza a las tres semanas, se sentó solo a los cuatro meses y el desarrollo mental parecía normal hasta que llegó a la edad de seis meses. Los ataques cerebrales volvieron a aparecer a los 5 meses y pronto después se notó una marcada deterioración. A los 12 meses cuando se le operó, no pudo levantar la cabeza y estaba completamente apático. Después los ataques desaparecieron y se notó el mejoramiento tanto mental como físico.

El paciente tiene ahora 8 años de edad. No ha tenido convulsiones desde que tenía 15 meses (3 meses después de la operación.) Está en el segundo grado. Tiene una edad cronológica de 8 años 4 meses, una edad mental de 6 años 2 meses, y un cociente de inteligencia de 69%.

601 N. Broadway, Baltimore 5

STREPTOMYCIN INTRAMUSCULAR DOSAGE PER UNIT BODY WEIGHT CORRELATED WITH SERUM LEVELS IN INFANTS AND CHILDREN

By ANDREW D. HUNT, JR., M.D., AND MARY B. FELL, B.S.
Philadelphia, Pa.

SERUM levels resulting from varying doses of streptomycin have been well worked out in adults.[1-8] It has been ascertained that the antibiotic is excreted in the urine by glomerular filtration alone,[1, 2] and that serum levels greater than the sensitivity of most organisms can, in general, be maintained for four to six hours following intramuscular injections of 500 mg. Alexander[9] has found that, in children, 44 mg./kg. body weight per day divided into eight doses given at three hour intervals gave blood levels ranging from 3.3 to 30.6 μg./ml. when the blood was drawn three hours after the final dose. However, there are no published studies concerning the serum levels in infants and children following intramuscular injections of varying amounts, nor has it been determined whether definite dosage per unit of body weight can be depended upon to produce predictable serum levels. In order to find the answer to some of these problems, and in an attempt to determine the most economical and least laborious schedule of streptomycin dosage for infants and children, the following study was undertaken.

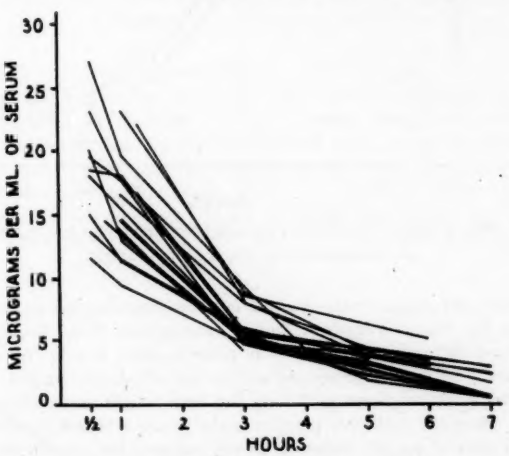

FIG. 1. Serum levels following single intramuscular injections of streptomycin 6.6 mg./kg. body weight.

METHODS

Standard commercial brands of streptomycin HCl and sulfate were used. Final dilutions of 50 or 100 mg. of streptomycin/ml. distilled water were prepared. Water was measured with a volumetric

From The Children's Hospital of Philadelphia (Department of Pediatrics, School of Medicine, University of Pennsylvania), Philadelphia, Pa.
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pipette. Standard 1 ml. or 2 ml. syringes with 22 gauge intramuscular needles were used for the injections, which were always given into the lateral aspect of the thigh.

The microtechnic previously described[10] was used for the assay of serum levels.

Preliminary trials showed that 6.6 mg./kg. gave serum levels comparable to those produced in adults by the customary dose of 500 mg. Single doses of this amount were consequently injected into 18 subjects ranging in age from 1 mo. to 12 yrs., and in wt. from 3 kg. to 41.4 kg. Patients for the most part were recovering from acute infections, and all were free of renal or cardiac disease.

Results are shown in Figure 1. The peak serum level is found in ½ hr., and ranges from 11.5 to 27.0 μg./ml. At the end of 3 hrs., the level has fallen to between 4 and 9 μg./ml. By the end of 4 hrs., the majority of levels are less than 5 μg./ml.; at the end of 7 hrs., the levels are all less than 3 μg./ml.

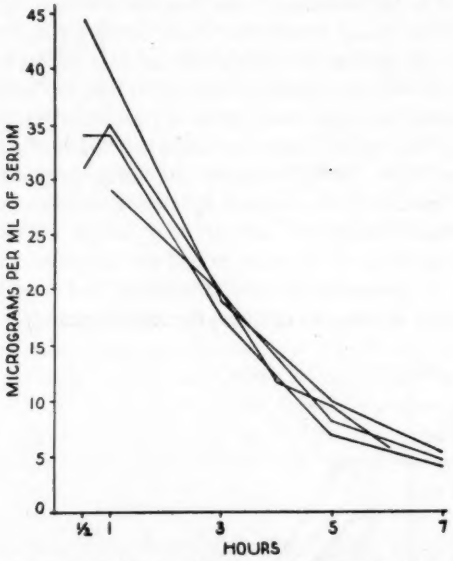

FIG. 2. Serum levels following single intramuscular injections of streptomycin 11 mg./kg. body weight.

Figure 2 illustrates the serum levels obtained in 4 patients after the intramuscular injection of streptomycin 11 mg./kg. The peak levels are higher, ranging from 27 μg. to greater than 35 μg./ml. With this larger dose, the peak level seems more prone to occur at 1 hr. At 3 hrs., the levels are much higher than in the 6.6 mg./kg. group, and at 6 hrs. are still above 5 μg./ml.

Four patients were given streptomycin 15.4 mg./kg. body weight intramuscularly, with the results shown in Figure 3. There is considerable variation in the ½ and 1 hr. levels, with 2 subjects showing peak values greater than 35 μg./ml. However, at 3½ and at 7 hrs., the levels are not significantly higher than those found at these intervals after doses of 11 mg./kg.

Single injections of 6.6 mg./kg. were given to 5 newborn infants. The babies were full term and healthy, and varied in wt. from 2.6 kg. to 3.8 kg., and in age from 2 to 6 days. All were moderately to slightly below their birth wt. at the time of the experiment. Results are shown in Figure 4. The peaks at ½ hr. range from 18.5 to 24.5 μg./ml., which is identical with the levels obtained in older babies and children. However, the levels are maintained longer than in the older group. At 3 hrs., the levels range from 8 μg. to 13.5 μg./ml., and at 6 hrs. the majority are greater than 5 μg./ml.

Serum levels resulting from intermittent intramuscular injections of streptomycin 6.6 mg./kg. were determined in 3 babies. They ranged in age from 5 to 21 mos., and in weight from 4 to 12.7 kg.

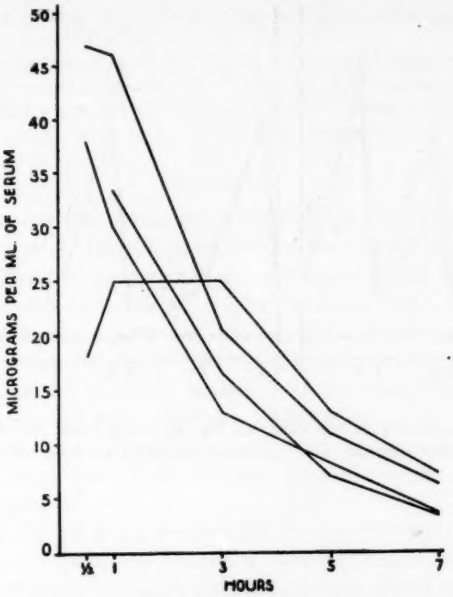

FIG. 3. Serum levels following single intramuscular injections of streptomycin 15.4 mg./kg. body weight.

They were recovering from acute illnesses, and showed no evidence of renal or cardiac disease. 6.6 mg./kg. were given every 3 hrs. for 24 hrs., after which time the interval was lengthened to 6 hrs., and the experiment was continued for 24 hrs. longer. During the second 24 hr. period, the experiment had to be discontinued in 2 patients. One was suddenly discharged from the hospital; the other developed an otitis media, and was given penicillin, which inhibits the growth of the test organism and invalidates the assay method. There is a slight cumulative effect which seems to reach a maximum after the 4th dose. After 24 hrs. of giving streptomycin every 3 hrs., the peak levels are no higher than after the 4th dose. However, there is a change in the rate of disappearance from

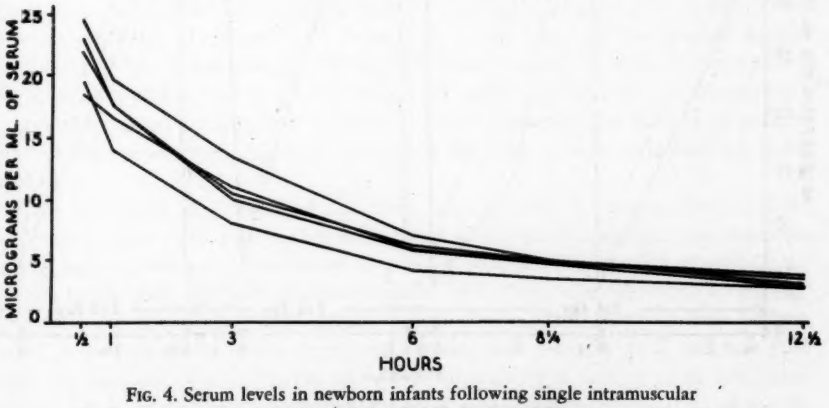

FIG. 4. Serum levels in newborn infants following single intramuscular injections of 6.6 mg./kg. body weight.

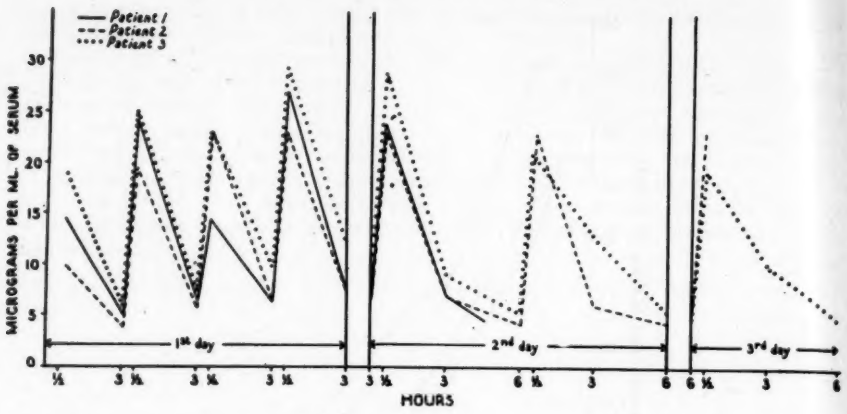

FIG. 5. Intermittent intramuscular injections, 6.6 mg./kg. every 3 hrs. for 24 hrs., and every 6 hrs. for subsequent 24 hrs. Injections were continued during periods indicated by breaks in curves.

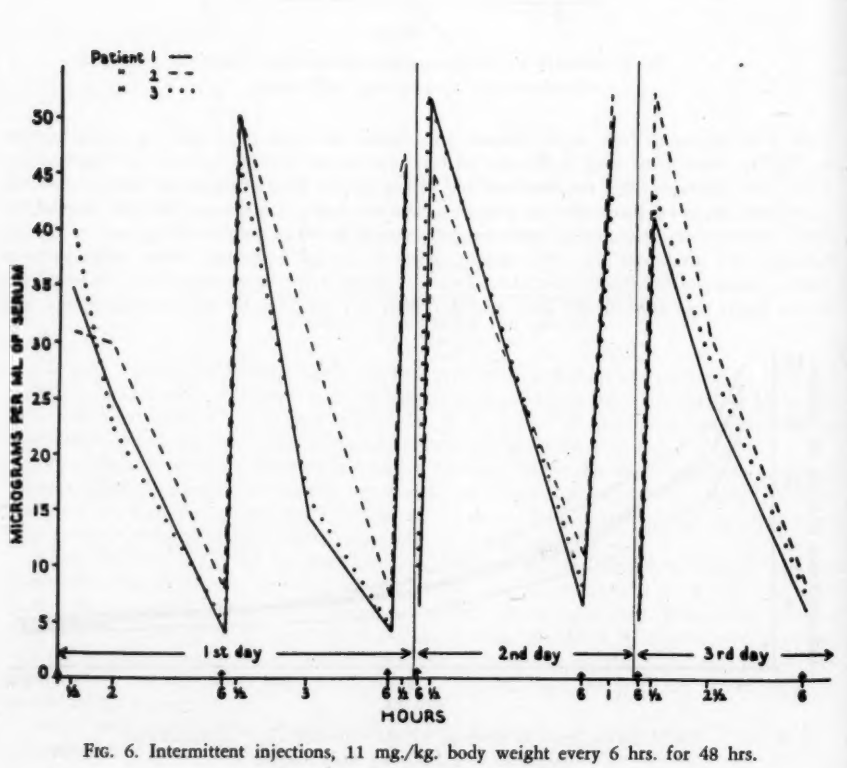

FIG. 6. Intermittent injections, 11 mg./kg. body weight every 6 hrs. for 48 hrs.

the blood stream, for serum levels of more than 5 μg./ml. are present 6 hrs. after each injection. These results are illustrated in Figure 5.

Intermittent intramuscular dosage of 11 mg./kg. every 6 hrs. was carried out in 3 subjects for a period of 48 hrs. Subjects ranged in age from 9 to 18 mos. and in wt. from 8.6 to 10.5 kg. (Fig. 6). The peaks are slightly higher after the 2nd injection, but there is little change in the levels at the end of succeeding 6 hr. periods. After 48 hrs. of this dosage schedule, there has been no significant cumulative effect.

Discussion

The peak levels observed here correspond to those reported in adults given single injections of 0.5 gm. Buggs et al.[3] found a serum level of 15 to 20 μg./ml. one hour after an injection of 0.5 gm. Zintel et al.[2] gave 0.6 gm. and obtained peak levels of 20 μg./ml. Anderson and Jewell,[1] also using 0.6 gm., found maximum levels of 12 to 14 μg./ml. Loewe and Alture-Werber,[6] using 0.5 gm., obtained serum levels after one hour of 17 μg./ml. Adcock et al.[5] recorded the weights of their subjects, and, although nearly all adults, there was considerable variation. Analysis of their results reveals that one subject received 6 mg./kg., and had a serum level at one hour of 18 μg./ml. Two subjects each received 11 mg./kg., and each had peak one hour levels of 32.5 μg./ml. This evidence tends to indicate that single doses of 6.6 to 11 mg./kg. body weight produce comparable serum levels in all age groups.

The delayed rate of fall in serum levels in the newborn babies is somewhat difficult to interpret. The immaturity of the newborn's renal function is one explanation for this phenomenon. Streptomycin is excreted primarily by glomerular filtration, and West, Smith and Chasis[11] have recently shown that, when correlated with surface area, glomerular filtration does not reach normal adult proportion until between the ages of 10 and 20 weeks.

This delayed fall in serum levels, however, seems to be limited to the newborn period. Several of the curves in Figure 1 represent serum levels in infants less than 20 weeks of age, and none has the slope seen in the newborns. It appears, therefore, that this delayed fall is a characteristic of the first few days of life. These newborn infants were all below their birth weights, and this fact, with consequent dehydration and low urine output, seems the most probable explanation for this finding.

Buggs et al.[3] gave six patients with good kidney function 500,000 to 1,000,000 u. of streptomycin every four or six hours, without significant accumulation in the serum. However, critically ill patients and those with severe renal disease showed marked cumulative effects. Loewe and Alture-Werber[6] report marked cumulative and additive effects, so that peak levels rose from 20 μg./ml. to 64 μg./ml. after 30 hours, when 0.5 gm. were given intramuscularly every six hours. However, the number of patients tested in their series, their degree of illness and the state of their renal function is not stated.

In the two series of intermittent injections here reported, the accumulation is slight and seems to reach its maximum after two or three injections. The effect is sufficient when 6.6 mg./kg. is given every three hours to make it possible after one day to prolong the intervals to six hours, and still maintain a serum level above 5 μg./ml. With 11 mg./kg. given every six hours, there was virtually no cumulative effect. None of these patients was ill at the time of the study, their renal function was clinically good and their fluid intake was adequate. A more marked cumulative effect could be anticipated in dehydrated children and those with impaired renal function. A more marked accumulation of strepto-

mycin in the serum of babies in the newborn period with intermittent dosage is also to be expected.

The necessity of maintaining a constantly high serum level of an antibiotic agent during the entire course of antibacterial therapy is at present being vigorously challenged.[12, 13] Zubrod[14] has recently shown that mice can be cured of K. pneumoniae infections with a therapeutic regimen in which there are long streptomycin-free intervals. That such is the case in gram negative infections in man has not been demonstrated. In any event, if it is desired to maintain serum levels above 5 μg. during the entire period of therapy, the dosage of 11 mg./kg. body weight intramuscularly every six hours appears to be satisfactory.

Summary

Predictable serum levels of streptomycin can be obtained by calculating dosage on a basis of mg./unit body weight. Dosage can be determined in this fashion in all age groups.

The serum streptomycin levels following single intramuscular injections of 6.6, 11.0, and 15.4 mg./kg. body weight are graphically illustrated.

The serum level following a single intramuscular injection falls more slowly during the newborn period. This is probably the result of dehydration and consequent low urine output.

Healthy children with apparently normal kidney function show little accumulation of streptomycin in the serum during intermittent intramuscular injection at the three and six hour intervals.

Eleven mg./kg. body weight every six hours is recommended as a satisfactory dosage schedule when it is desirable to keep the blood streptomycin level constantly above 5 μg. per milliliter.

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SPANISH ABSTRACT

Dosis de Estreptomicina Intramuscular por Unidad de Peso de Cuerpo en Correlación con Cantidades de Suero en Infantes y Niños

Cantidades de suero estreptomicina pronosticables pueden ser obtenidas calculando la dosis a base de mg./kg. peso de cuerpo. Se puede determinar la dosis de esta manera en los grupos de todas edades.

Intramuscularmente, 6.6 mg./kg. dan cantidades maximas de suero ½ hora después de inyecciones simples en graduación de 11.5 a 27.0 µg./ml. Se mantiene un nivel arriba de 5 µg./ml. por aproximadamente 3 horas. En infantes recien nacidos la bajada en la cantidad de suero es bastante tardada, así es que los niveles arriba de 5 µg./ml. se mantienen por lo menos 6 horas. Se cree que esta tardanza es el resultado de deshidratación y formación disminuída de orina en el período neonatal.

Dosis intramusculares simples de 11 mg./kg. producen cantidades máximas a la media hora en graduación de 27 µg./ml. Los niveles de 5 µg./ml. se mantienen por lo menos 6 horas. Las dosis mayores de 11 mg./kg. no parecen tener ninguna ventaja. Se producen cantidades máximas un poquito más altas con 15.4 mg./kg., pero después de 6 horas los niveles son exactamente idénticos a aquellos producidos por 11 mg./kg.

Las cantidades de suero arriba de 5 mg./ml. pueden ser mantenidas con una dosis intramuscular intermitente de 6.6 mg./kg. cada 3 horas, o con 11 mg./kg. cada 6 horas. El efecto cumulativo es insignificante siempre que la función renal no sea perjudicada y se mantenga la hidratación. Se cree que 11 mg./kg. cada 6 horas es una dosis satisfactoria para infecciones más agudas susceptibles a terapia de estreptomicina intramuscular.

1740 Bainbridge Street

ADVISING PARENTS OF EARLY STUTTERERS

By SPENCER F. BROWN, M.D.
Iowa City, Iowa

PROBABLY no other disorder which affects as many persons* as does stuttering has received so little attention from the medical profession, particularly in the United States. Quite likely physicians have felt that diseases more threatening to life demanded their attention. Stuttering has been widely regarded as a habit, however loosely this term be defined. As such, it may have been regarded as being more properly an object of study by educators and psychologists than by medical men.

Various nonmedical specialists have published well over 200 experimental studies on various aspects of stuttering. Unfortunately, little of this large mass of important material has appeared in medical journals, even in abstract form. In this paper an attempt will be made to summarize and interpret certain experimental studies and critical reviews to be found in nonmedical literature, particularly with regard to young "beginning" stutterers.

There have been many biochemical and hematologic studies comparing stutterers with nonstutterers. In a critical review, Hill[1] has summarized the results of these and other such investigations. The few consistent differences found include slightly higher blood calcium levels, RBC and WBC counts in stutterers. These differences are best explained in terms of greater activity of both smooth and striated muscle. During speech, stutterers exert greater effort than do nonstutterers, and this is reflected in the slight and comparatively insignificant differences found in Ca, RBC and WBC.

Investigators have compared stutterers with nonstutterers on many physiologic functions. In another critical review, Hill[2] has evaluated these physiologic studies. He demonstrates that the occasional small differences found between stutterers and nonstutterers are best explained in terms of the startle reaction. As a group, stutterers seem to react to certain situations with the same startle pattern as may be found in any human subject when a sudden adequate stimulus is applied. This set appears to be learned, rather than an inherent difference between stutterers and nonstutterers.

Beginning in 1938 there have been several crucial studies of the speech of preschool children, both stutterers and nonstutterers. As a result of this carefully performed research, a new theory of stuttering has developed, and a new technique for dealing with young stutterers.

Various investigators (Bluemel,[3] Van Riper[4]) had previously pointed out that stuttering as it is encountered in the adult differs greatly from that observed in young stutterers. The adult may have a long and elaborate series of reactions accompanied often by extreme degrees of tension in the muscles involved in speech. Usually the tension spreads to other muscle groups as well. The reader is familiar—either from direct observation of adult

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From the Speech Clinic, State University of Iowa, Iowa City, Iowa.
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* According to numerous surveys, about 1% of the total population stutters. The figure for the school age population is slightly higher.

stutterers or from the descriptions in the literature—with the many components of adult stuttering behavior: grimaces, eye blinking, tongue protrusion, jaw clenching, sweating, silent intervals, grunting, head jerking and a host of others. Contrasted with this tempest of activity, the stuttering of the early stutterer is placid indeed. His interruptions consist usually of repetition of a sound, syllable, word or phrase in an easy and effortless way. Occasionally there may be prolongation of a sound, again in a manner free from tension. The characteristic feature of this early stage is its ease, its lack of selfconsciousness. Despite all the worries of his family, the child is, at first, blissfully unconcerned.

Now if repetitions are the distinguishing characteristic of early stuttering, it is obviously in order to investigate them, to determine whether they differ from the repetitions often heard in the speech of nonstuttering children. Precisely this question was studied in a series of investigations. A group of 46 children, aged 2 to 11, who had been stuttering less than 6 months on the average was observed by Johnson et al.[5] It was found that these children presented the above-mentioned repetitions of single sounds, syllables, words and phrases. In most cases, these repetitions were found to be in no way different* from or more numerous than the repetitions in the speech of a group of "normal" preschool children who had been intensively studied by Davis.[6, 7] These latter also presented repetitions in their speech, ranging from single sound repetitions up to the repeating of entire sentences. There was one repetition for each 22 words on the average. The two groups presented about the same amount of repetition. Yet one was composed of "stutterers" and the other of "normal speakers."

At this point, it is pertinent to inquire how it was determined that the children in the first group were stutterers. Were the diagnoses made by speech pathologists or other presumed experts? In every case it was found that the diagnosis had been made by a person untrained in speech, usually a parent. Wide study shows this to be true of stutterers generally. Stuttering would appear to be a unique disorder in that it is always first diagnosed by a layman.

Since the two groups of children were objectively almost equal with respect to speech repetitions, it was entirely possible that there was no fundamental difference between them. To test this hypothesis, the parents of each child in the "stuttering" group were told that their child had been found on examination to be normal. It was explained that the repetitions their child presented were characteristic of the speech of all preschool children. If ignored, they would disappear. Considerable effort was made to convince the parents of the essential normality of their child's speech. Follow-up studies showed 72% of the original stuttering group presented normal speech 30 months later on the average.[5] In general, the parents of those children who were still stuttering had been resistant to the explanations given them and had not acted upon the speech pathologist's advice.

Out of these and other studies and therapeutic tests, a new theory of stuttering was developed by Wendell Johnson, Director of the University of Iowa Speech Clinic. It has been described by him in various publications, particularly in *People in Quandaries*[8] and *Speech Handicapped School Children*.[9] It will be briefly presented here, without elaborate documentation.

Johnson's theory holds that the most common and significant cause of stuttering is the diagnosis thereof. Davis'[6, 7] and following studies[10] included over 200 different

* In a few cases there were the beginnings of the tensions characteristic of the adult stutterer.

"normal" preschool children, every one of whom was found to have repetitions in his speech. This is a surprising fact to most persons. Apparently the normal repetitions of preschool speech are so familiar that they are usually ignored. Now and then a parent becomes aware of his child's occasionally repetitive speech, and decides that it is abnormal. He labels his child a "stutterer," even though he may not at first communicate this diagnosis to anyone else.

Having decided that his child is doing something abnormal, the parent now begins to react to the label he has applied. He winces when he hears any repetition, and often expresses concern over it. The other parent is asked to listen for the "stuttering." The child may be urged to "slow down," to "stop and start over," "think what he wants to say." He is told to take a deep breath before he begins to talk. He may be simply told to "stop stuttering," and even punished for speech repetitions.

Sometimes the parents decide to say nothing about the repetitions in the hope that they will cease. But since they are convinced that repetitions are abnormal, they develop a good deal of tension and worry about the child's speech, and usually they are unsuccessful in concealing their concern. Before long one of the parents betrays the cause of the increasing tension within the family, and the child knows what has been the matter.

In any case, the child soon learns that any speech repetition is undesirable. His parents don't like it. A beseeching look from a distraught parent teaches just as quickly as a slap in the mouth. So he tries to avoid repetitions, and to speak with perfect fluency. This is impossible for him, as it is for any child. As he continues his attempts, several unfortunate things occur.

First, the child begins to be oppressed by a sense of failure. He is frequently unable to speak as fluently as he feels he should.

Second, he begins to fear talking in those situations in which penalties for repetitive speech are likely to be more severe.

Third, he begins to use excessive strain and tension in talking in an effort to avoid any sort of nonfluency. The effect of this added muscular tension is to prolong any interruption that occurs. Thus a vicious circle is set up: tension causes prolonged interruptions resulting in greater concern and still greater tension, etc. From these early efforts to eliminate a normal and harmless repetition come the innumerable phenomena of adult stuttering.

It is somewhere in this early stage that parents most often seek advice. The proper sort of help takes a good deal of time, but yields gratifying results.

The first essential is a detailed history of the "stuttering." When was it first noticed, and by whom? What measures have been taken to eliminate it? How much repetition had the child been doing before the parents decided it was stuttering? It is important to disregard any statements of the parents to the effect that there was "absolutely no repetition until such and such a date." Histories of dramatic and sudden "onset" must be interpreted as indicating the first awareness on the part of the parents that their child's speech contained repetitions and not as a sudden beginning of those repetitions. Parents who have unrealistically high speech standards for preschool children often have other rigid ideas. It is well to inquire into the parents' standards in matters of discipline, such as toilet training. Family histories of other stutterers in the stock do not indicate an inheritance of stuttering, but rather explain why the parents were anxious that their child's speech be perfect.

It is important to find out what explanations and theories the parents have to account for the speech difficulty. The most popular explanation is that the child "thinks faster than he can talk," and is usually offered with an air of pride in this evidence of the child's superior intelligence. A close second is that he "talks faster than he can think." "Nervousness" is another favorite theory. When this is given, one should seek the basis of the tensions and insecurities in the home that cause the "nervousness." Parents who proudly insist that their child is "high-strung" are especially likely to suffer themselves from anxieties and maladjustments of various sorts. Though most of the questions asked relate to the child, the real purpose of the history is to secure an understanding of the parents. Needless to say, the child should not be present during the taking of the history.

Complete physical examination should be routine. It will not, of course, reveal the cause of the stuttering, but it enables the parents to accept positive reassurance that no organic abnormality is related to the stuttering.

Speech examination should be carried out in two parts: in the parents' presence and with the child alone with the physician. The behavior of the parents during the child's nonfluencies should be observed, and the child's reactions to their behavior. The presence of tension during repetitions should be noted, and whether there are other forms of interruptions, such as tonic blocks, prolongations of sounds, and excessive use of "uh" or "ah." Facial grimaces and tension in parts of the body other than the speech mechanism should be watched for.

When examining the child alone, the physician should be as informal as possible. Since the child is already suffering from too much pressure on his speech, the physician must be careful not to appear to be forcing the child to talk. At the conclusion of the speech examination, the child should be given brief but firm reassurance, and then dismissed while the physician returns to counsel the parents.

The basis of the first counselling session following the history and examinations is a discussion of the theory of stuttering herein presented. At the Iowa Speech Clinic, this occupies approximately an hour. The development of speech is first discussed briefly, and the normality of repetitions in infant and preschool speech is strongly emphasized. The way in which diagnosing normal repetitions as stuttering leads to tension and anxiety is discussed.

Through all this discussion, care is exercised to allay parental guilt reactions. Many parents feel that they are being "accused" of causing their child's stuttering. One must tactfully point out that whatever mistakes the parents made were the result of genuine concern and a sincere but misguided attempt to "improve" their child's speech. Millions of others have made the same mistake. In the presence of what he regards as a defect in his child, any loving parent will try to do everything he can to correct it. He must not be permitted to blame himself for his misdiagnosis or his unfortunate "treatment." Only a few parents are trained in speech pathology.

If the child is showing little or no tension in his moments of nonfluency, the parents are advised that such interruptions are within or close to normal limits, and are in no sense a cause for concern. Strict injunctions are given against expressing any sort of disapproval of nonfluency. If the parents and others in the child's environment do not react at all to the repetitions, the child himself will eventually cease to react, and the repetitions will no longer be a problem to the child or to anyone else. More important than the elimination of the parents' overt reactions to nonfluency is the more fundamental

business of changing their notion that their child's speech is abnormal. If they persist in their notion that the child "is not talking the way he should," their efforts to suppress overt disapproval of interruptions will be only temporarily and partially successful. The parents must unreservedly accept the assurance that their child's speech is essentially normal if they are to stop worrying about it.

This is by no means the same as telling the parents to "forget about it," or that the child will "outgrow" his nonfluency. Such ill-considered advice is too often given. But it fails completely to relieve the parents' concern. It does not alter their conviction that the child's interruptions are abnormal, for they have no basis on which to think otherwise. They cannot "forget it"—and they don't. Actually, we do not wish them to "forget" the interruptions. We simply want them to evaluate them properly. Further conferences and discussions are usually needed, and the parents are usually requested to make careful observations of conditions under which the child's nonfluencies occur. Eventually, of course, as a result of alleviation of anxieties, the parents cease to notice most if not all of the child's repetitions. This goal can only be approached gradually and indirectly.

If the history has disclosed parental over-solicitude, improper standards or methods of discipline, or other such problems, it is best to defer attempts to correct these until succeeding conferences, but they should not be ignored. Every effort should be made to render the child's home environment as favorable as possible.

Ideally, the parents should be seen several times at intervals of two to three weeks. After this, if no complicating problems require more frequent visits, several follow-up conferences at three to six month intervals are suggested. For the second conference, assignments are often given the parents. They are instructed to make detailed observations on the speech of children outside the family whom they regard as nonstutterers. They are asked to count the repetitions heard in 5 or 10 minutes, for example. They may also be asked to observe nonfluencies in informal, extemporaneous adult speech. These assignments help to convince the parents of the soundness of the statements that have been presented to them.

Drug treatment is strictly contraindicated. Phenobarbital is frequently prescribed for stutterers, but from the foregoing discussion it is obvious that such medication is irrational and harmful. It tends to reinforce the parents' feeling that something is seriously wrong with the child. Quite apart from the theory and therapy herein presented, it may safely be said that none of the long list of drugs occasionally given to stutterers has any rational basis or any adequate proof of clinical effectiveness.

Like any other therapy, that outlined above has its failures. These almost always occur when the parents, for whatever reason, are unwilling or unable to accept the explanation given them. It is usually possible to predict after the first or second conference whether the parents are going to be able to stop their pressure on their child's speech and thus permit him to escape further difficulty. Many of these failures are the fault of the therapist. If he arouses serious guilt feelings in the parents, they may reject his explanation so as to escape the burden of guilt. But the most tactful and skillful physician will be unable to convince some parents.

It should be emphasized that this therapy is designed for those children who have not developed anxieties concerning their moments of nonfluency and marked muscular tensions during those moments. It is adequate treatment for these cases only. Children who have become confirmed stutterers—those in whom significant anxiety and tension are

present—almost always benefit from improving the psychologic environment and elimination of expressions of parental disapproval of nonfluency. However, they almost always need additional treatment in the form of direct help from a speech correctionist. If a qualified speech clinician is not at hand, information should be sought from the American Speech and Hearing Association. This Association is the recognized national organization of speech correctionists and it sets up standards for training and certification. The office of the Secretary-Treasurer is located at Wayne University, Detroit, Michigan.

It should also be emphasized that stuttering is but one of the various types of speech defects found in childhood. The therapy herein outlined is appropriate only for beginning stutterers. It should not be applied to other types of defects.

Summary

A brief review of a number of research studies on stuttering is presented. Physiologic and biochemical differences between stutterers and nonstutterers were found to be slight or absent. The increased muscle tension and the startle reaction pattern of most adult stutterers explain the differences found.

Research has shown that repetition is normally present in the speech of preschool children. Parents or other persons may mistakenly diagnose this repetition as stuttering. Such a misevaluation leads to unwarranted concern over the child's speech and disapproval of his repetitions. In a vain effort to eliminate nonfluency, the child develops tension which increases the frequency and duration of the moments of nonfluency. Therapy for the beginning stutterer is directed at the parents, and takes the form of education as to realistic standards for speech of preschool children generally, and reassurance as to the essential normality of their own child's speech.

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Spanish Abstract

Aconsejando a los Padres de Tartamudos Tempranos

Presentamos aquí una breve reseña de algunos trabajos de investigación sobre el tartamudeo. Las diferencias fisiológicas y químicas que se han encontrado entre tartamudos y no tartamudos, son pequeñas o inexistentes. El aumento de la tensión muscular y la conducta de la reacción "startle," que experimentan la mayoría de los adultos tartamudos, explican tales diferencias.

La investigación ha mostrado que la repetición se presenta normalmente en el habla del niño en edad preescolar. Los padres u otras personas pueden diagnosticar erróneamente esa repetición como tartamudeo. Semejante juicio equivocado conduce a una injustificada preocupación por el habla del niño y a la desaprobación de sus repeticiones. En un vano esfuerzo por eliminar la falta de soltura, el niño desarrolla una tensión que aumenta la frecuencia y la duración de los momentos de falta de fluidez. A los padres va dirigida la terapéutica en los casos de tartamudos principiantes y trata de educarlos respecto de los standards realistas del lenguaje de los niños en edad preescolar, en general, y, también, de reafirmarlos respecto de la normalidad esencial del habla de sus propios hijos. También importante es el intento de corregir los problemas que suscitan la disciplina demasia do severa o demasiado laxa, el cuidado excesivo, etc.

Esta terapéutica es sólo adecuada para los niños que no ponen de manifiesto una ansiedad muy vehemente en esos momentos de falta de fluidez ni, tampoco, una marcada tensión muscular durante tales momentos. Si la ansiedad y la tensión existen, aun cuando las medidas indirectas descritas más arriba sirvan de alguna ayuda, es indicado un tratamiento directo del habla del niño. Un clínico del habla experto puede ser de gran valor.

La terapéutica descrita es apropiada sólo en el comienzo de la tartamudez. No debe recurrirse a ella para la curación de los otros tipos de defectos del habla que se encuentran en la niñez.

University of Iowa

PROTEOLYTIC ENZYMES OF THE PREMATURE INFANT

With Special Reference to His Ability to Digest Unsplit Protein Food

By STEPHEN MADEY, M.D., AND JOSEPH DANCIS, M.D.
New York, N.Y.

FOR years it has been generally accepted that breast milk represented the ideal food for the premature infant. Recent metabolic studies,[1-7] however, have raised considerable doubt that the food designed by nature for the full term infant is also best suited to the unusual requirements of the premature, and as a result of these studies a formula richer in protein and minerals than breast milk has been advocated. The further suggestion has been made by Swedish investigators that the premature infant may have difficulty in digesting protein food, and that feeding with protein hydrolysates is desirable. Magnusson and his collaborators[8, 9] observed more rapid weight gains on breast milk reinforced with casein hydrolysate than on breast milk reinforced with casein. Schürer[10] conducted a similar, but not as well controlled, study. Werner[11] reported a deficiency of the proteolytic enzymes of the stomach and pancreas in the premature. The enzyme studies of Werner were made exclusively on tissues obtained at post mortem. Since the question raised by them is one of fundamental importance it seemed desirable to confirm these clinical observations and also to measure the proteolytic enzymes of duodenal juice *in vivo*, data which cannot be found in the literature.

ENZYME STUDIES

Duodenal drainage was carried out on 16 premature infants weighing between 1120 and 1790 gm. The procedure was carried out as soon after birth as the condition of the infant permitted.* A sterile catheter (#10 French) was passed by mouth and slowly guided into the 1st portion of the duodenum under direct fluoroscopic visualization. Fluid was permitted to drain through the tube spontaneously, the results of suction being disappointing. As a rule, bile-stained fluid appeared within ½ hr. Drainage was continued until 2 cc. had been collected for analysis. The sample was then placed on ice and analyzed for trypsin within 6 or 8 hrs., using the modification of the Fermi method described by Andersen.[12] This method is based on the ability of the sample to liquify a standard preparation of gelatin, the drainage sample being set up in various dilutions.

Results: All drainage fluids produced good liquefaction with the equivalent of 0.01 cc. duodenal juice and 12 of the 16 samples showed activity with 0.005 cc. These findings indicate normal trypsin values approximating 200 viscometric units per cc. or better.[13] These studies, therefore, fail to support the contention that the premature infant secretes inadequate quantities of proteolytic enzymes in his digestive tract.

CLINICAL OBSERVATIONS

It seemed desirable to supplement these laboratory findings with studies on the weight gain of premature infants using alternate supplementation of the feeding with whole casein and casein hydrolysate, as had been done by Magnusson et al. Sixteen infants were included in this study. All

From the Department of Pediatrics, New York University-Bellevue Medical Center, New York, N.Y.

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* Drainages were done at the following ages: R.G., 2 days; G.B., 3 days; M.C., F.R. and M.P., 4 days; D.F., H.K., M.S. and L.A., 5 days; R.M., 7 days; P.K. and B.S., 9 days; E.K., 11 days; F.M., 13 days; S.S., 16 days; J.P., 23 days.

had birth weights below 1800 gm. and, apart from prematurity, were normal infants, with complications being excluded from the study. Fourteen of these infants were included in the enzyme study previously described.

The infants were grouped in pairs of comparable birth weight, sex and race. One member of the pair would then be given the formula reinforced with whole casein and the other the formula reinforced with casein hydrolysate. At 10 day intervals the feedings were reversed.

The basal feeding to which the 2 supplements were added differed from that employed by Magnusson in that it consisted of cow's milk in which corn oil had been substituted for the butter fat in

TABLE I

AVERAGE DAILY WT. GAIN OF PREMATURE INFANTS FED ALTERNATELY ON CASEIN REINFORCED MILK (CR) AND ON MILK REINFORCED WITH CASEIN HYDROLYSATE (HR)

Case	Birth Wt. (gm.)	1st–10th day		11th–20th day		21st–30th day		31st–40th day	
		Formula	Gain (gm.)	Formula	Gain (gm.)	Formula	Gain (gm.)	Formula	Gain (gm.)
H.K.	1120	CR	−140	HR	140	CR	155	HR	255
J.D.	1190*	HR	?	CR	285	HR	370	—	—
J.O.D.	1290*	CR	?	HR	255	CR	285	—	—
R.M.	1290	HR	−140	CR	170	HR	170	CR	425
L.A.	1390	CR	− 30	HR	200	CR	370	HR	285
M.C.	1290	HR	0	CR	285	HR	310	CR	285
R.G.	1390	CR	−250	HR	240	CR	395	HR	310
F.M.	1640	HR	−200	CR	255	HR	285	CR	340
S.S.	1670	CR	−370	HR	200	CR	255	HR	310
F.R.	1670	HR	−200	CR	170	HR	255	CR	310
G.B.	1730	CR	−115	HR	285	CR	225	—	—
B.M.	1730	HR	−170	CR	255	HR	285	—	—
P.K.	1790	CR	−170	HR	225	CR	255	HR	310
M.S.	1790	HR	−170	CR	170	HR	285	CR	340
E.K.	1800	CR	− 15	HR	200	CR	370	HR	285
E.L.	1800	HR	−100	CR	210	HR	290	CR	450
Average daily gain on CR			−156		225		289		358
Average daily gain on HR			−140		218		281		293

* Infant not weighed until 3rd day of life.

order to increase the fat assimilation: the "casein reinforced" feeding prepared from this consisted of the commercial product Olac in which the "corn oil milk" has been supplemented by the addition of calcium caseinate;* the "casein hydrolysate reinforced" feeding was identical with Olac with the exception that a pancreatic digest of casein (Amigen) had been substituted for the casein supplement in comparable amounts.† In this feeding, roughly ⅓ of the protein moiety is supplied in hydrolyzed form.

* Olac is a spray dried powder consisting of skimmed milk solids 40.6%, dextrimaltose 31.7%, corn oil 17.5%, halibut liver 0.1%, and casein 10.1%.

† By analysis, the nitrogen content of the Olac was found to be 3.67%. The nitrogen content of the Olac-amigen was 3.53%, and of this the amigen supplied 1.29%. The calcium content of the two preparations was 0.7%.

Both the "casein reinforced" feeding (Olac) and the "casein hydrolysate reinforced" feeding (Olac-amigen) were supplied by Mead Johnson and Company through the courtesy of Dr. Warren M. Cox, Jr., who also made the analyses of their calcium and nitrogen content.

Feeding schedule, regardless of the formula used, was as follows:
First 12 hrs.: nothing by mouth
12 to 24 hrs.: lactose water only
2nd to 4th day: 10 cal./lb. (22 cal./kg.)
5th to 7th day: 20 cal./lb. (44 cal./kg.)
8th to 10th day: 30 cal./lb. (66 cal./kg.)
11th to 13th day: 40 cal./lb. (88 cal./kg.)
14th to 16th day: 50 cal./lb. (110 cal./kg.)
17th day onward: 60 cal./lb. (132 cal./kg.)

Results: In Table I are given the weight gains of infants on the casein reinforced (CR) and the casein hydrolysate reinforced (HR) formula.

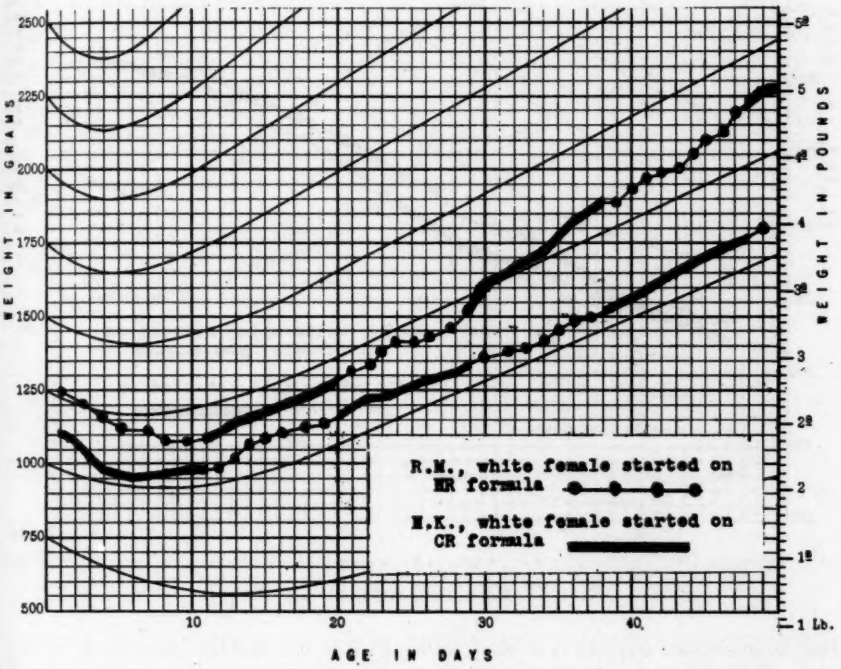

FIG. 1. Wt. curves of infants fed casein reinforced (CR) formula alternating with casein hydrolysate reinforced (HR) formula.

Some representative wt. curves are shown in Figures 1 and 2. The curves are smooth and show no acceleration during the periods of supplementation with hydrolysate. Both wt. curves and tabulated data fail to reveal any significant difference in wt. gain on these 2 feedings during the 1st mo. of life. The significance of the greater wt. gain on the casein reinforced feeding between the 31st and 40th day may be questioned because of the smaller number of observations at this time.

In addition to these observations, 4 infants were fed on the casein hydrolysate reinforced feeding throughout their stay in the hospital, their wt. curves being compared wth the expectancy curves obtained from previous experience with a casein reinforced feeding.[14] Graphs of these 4 patients show no significant deviation from the experienced wt. gain on casein supplemented feedings. Wt. curves of 2 of these infants are shown in Figure 3. Wt. curves of 2 infants of similar birth weight and sex fed only casein reinforced milk are also graphed.

Conclusions

The data presented indicate that premature infants do as well on the whole casein as on the casein hydrolysate feedings, and reveal no shortage of trypsin in the duodenal juice. The discrepancies between these findings and those of the Swedish investigators deserve some comment. There is no reason to question enzyme assays of Werner, but it may be doubted whether conditions found in premature infants who have succumbed from causes not stated should be taken as representative of premature infants as a whole. Moreover, a diminished content of enzyme in a digestive gland does not per se imply

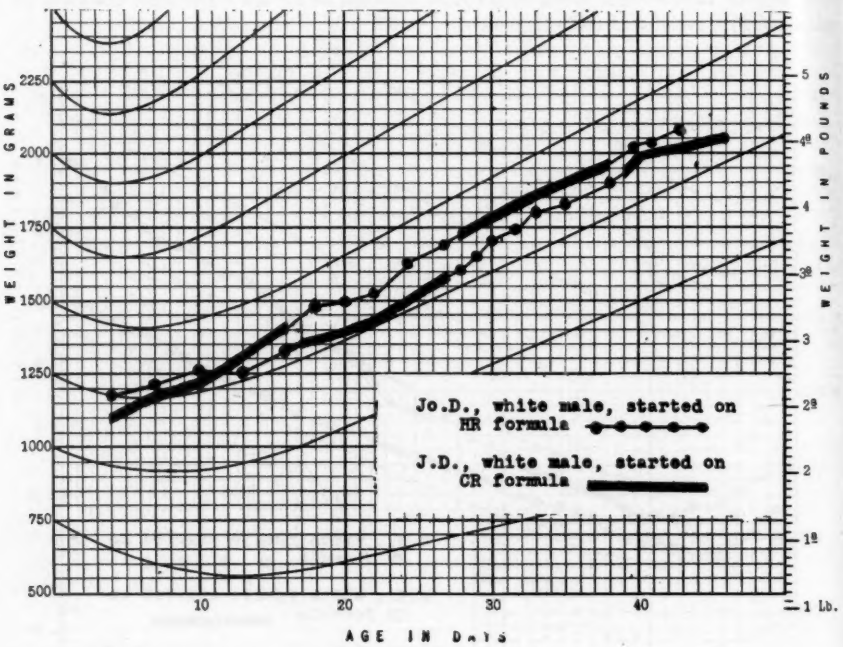

Fig. 2. Same as Fig. 1.

that an inadequate quantity is secreted. Although it is true that the observations in this study dealt with concentrations of enzyme secreted rather than total quantity, the latter being impractical to measure, the fact that no difficulty was experienced in collecting 2 cc. samples in a reasonable length of time suggests that the quantity of duodenal juice secreted was adequate.

In comparing these clinical results with those of Magnusson et al., it may be noted that these diets differed from those of the Swedish workers in that breast milk was used as the basis of their diets rather than cow's milk, with the result that all their observations were made at a lower level of protein intake. It is conceivable that at marginal levels of nitrogen intake differences might appear which can not be detected when a higher level of protein is given. However, the evidence obtained here, that the duodenal juice of the premature infant can split protein, readily speaks against the need for predigested protein food.

A point that must be considered is the species difference in the composition of the casein of cow's milk and human milk.[15] Another difference lies in the preparation of the

casein supplement. Magnusson used casein purified by isoelectric precipitation. This substance is less soluble than the calcium caseinate used to supplement the olac. It is conceivable that this may have affected the results; however, there is no data on the relative ease of utilization of the two products.

The limited data here, showing slightly better performance on casein than on hydrolysate after the 30th day of life, certainly do not permit the conclusion that whole casein

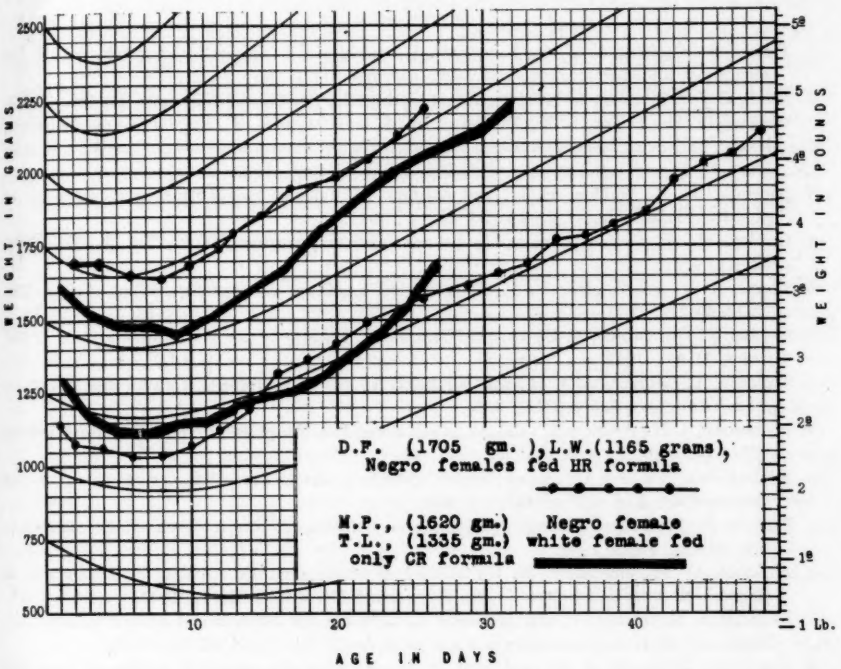

FIG. 3. Wt. curves of 2 infants fed only casein hydrolysate reinforced formula (HR) compared with 2 infants fed only casein reinforced formula (CR).

is superior, but it is only proper to mention some data on experimental animals suggesting that nutritionally valuable complexes may be lost during the process of hydrolysis. The observations of Woolley[15] on the importance of the polypeptid complex designated as strepogenin stand out here. It should be pointed out that the need for such complexes is still a controversial matter. Some evidence exists[16] that there are species differences in this regard and little is known about the human species.

Although it is clear that normal growth and nitrogen retention[17] can be obtained in infants with casein hydrolysates, no long term studies with such feedings are as yet reported. These considerations and the results of this study just recorded make it difficult to accept the conclusions of Magnusson as to the desirability of substituting split for unsplit protein in the dietary of the premature infant.

SUMMARY

The duodenal contents of 16 premature infants were examined and found to contain normal concentrations of trypsin. The gain in weight of infants whose diet was supple-

mented with casein hydrolysate was found to be no better than that of infants supplemented with whole casein. It is concluded that it is unnecessary to supplement the diet of the premature with split protein.

ACKNOWLEDGMENT

Acknowledgment is made to Dr. L. Emmett Holt, Jr., for his valuable suggestions in the preparation of this paper.

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SPANISH ABSTRACT

Enzimas Proteolípticos del Infante Prematuro con Refcrencia Especial a su Abilidad de Digerir Alimento Proteina Entero

Se examinó el contenido duodenal de 16 infantes prematuros y se encontró que contenía concentraciones normales de tripsina. Se descubrió que el aumento en peso de los niños, cuya dieta estaba suplementada con caseína hidrolizada, no era mejor que el de los infantes cuya dieta estaba suplementada con caseína entera. Se llegó a la conclusión que no es necesario suplementar la dieta del infante prematuro con proteína dividida.

492 First Avenue

CHRONIC INTUSSUSCEPTION

By HENRY A. REISMAN, M.D., AND ARTHUR D. WOLK, M.D.
Jamaica, N.Y.

THE proper and prompt diagnosis of intussusception constitutes one of the important emergencies in pediatric practice. The acute type, however, does not present as great a diagnostic problem as does chronic intussusception. Its diagnosis is usually facilitated by the classical symptomatology of colicky pain, vomiting, abdominal distension with blood and mucus in stools occurring in a male infant. Chronic intussusception, on the other hand, presents no such typical picture. In fact, evidence pointing to it is often vague and the signs of intestinal obstruction are frequently lacking.

It is with this consideration that the following two cases of chronic intussusception of differing location and etiology are presented.

CASE REPORTS

Case 1. W.B., 5 yr. old white male, was admitted to the Pediatric Service of Queens General Hospital on December 3, 1947 because of abdominal pain of 8 wks.' duration. Pain was localized to the para-umbilical region, intermittent and colicky in nature. Attacks were of 5 to 10 secs. duration, recurring frequently throughout the day except in the 2 wks. prior to admission when the incidence decreased to about 1 attack every 3 days. Pain was not related to or influenced by excitement, emotion, food, defecation, micturition or diversion.

The only episode of vomiting occurred 4 days prior to admission. At the onset of the present illness, patient had mild constipation easily relieved by enemata. This was followed by mild diarrhea. In the wk. prior to hospitalization, the mother noted dark red blood in the stools. Patient had anorexia, wt. loss of 3.2 kg. and complained of fatigue and lethargy. At times he had a low grade temperature up to 38.2°C.

There was no history of dietary indiscretion or idiosyncrasy. No allergic manifestations had ever been noted in either the patient or his family.

Physical examination revealed a malnourished, almost emaciated, boy of 5 yrs., weighing 12.2 kg. and appearing chronically ill. Patient did not appear to be in any acute discomfort. Examination of the abdomen revealed a flat contour without masses, tenderness or rigidity. Normal bowel sounds were heard. Rectal examination was negative.

Temperature was 37°C., pulse 100, and respiration 24. Blood pressure was 98 systolic, 60 diastolic. Examination of the blood revealed RBC 3.8 million/cmm., Hgb. 12 gm./100 cc. and WBC 17.8 thousand/cmm., with neutrophiles 90%, lymphocytes 6%, monocytes 3% and eosinophiles 1%. Urine gave a positive test for acetone. Benzidine test was positive for occult blood in the stools, but stools were repeatedly negative for ova, parasites and pathogenic bacteria.

Nose and throat cultures as well as blood cultures were negative. Agglutinations for typhoid, paratyphoid and brucellosis were negative. Wassermann and Mantoux reactions were negative. Blood chemistries revealed calcium 11.6 mgm.%, phosphorus 4.8 mgm.%, cholestorol 165 mgm.% and sugar 100 mgm.%. Erythrocyte sedimentation rate was 24 mm./hr. (Westergren method).

In the hospital, patient had infrequent attacks of pain as previously described. Examination of the abdomen during and immediately after these attacks was negative. There were 3 brief episodes of emesis. Stools were soft, occurred about once daily, and were occasionally blood streaked.

Roentgenographic study revealed no significant findings in the chest plate or flat plate of the abdomen. Excretion urography was negative. Barium meal, including fractional small intestinal study, revealed a normal mucosal pattern up to 3 hrs. Barium enema examination (see Fig. 1)

From the Department of Pediatrics, Queens General Hospital, Jamaica, N.Y.
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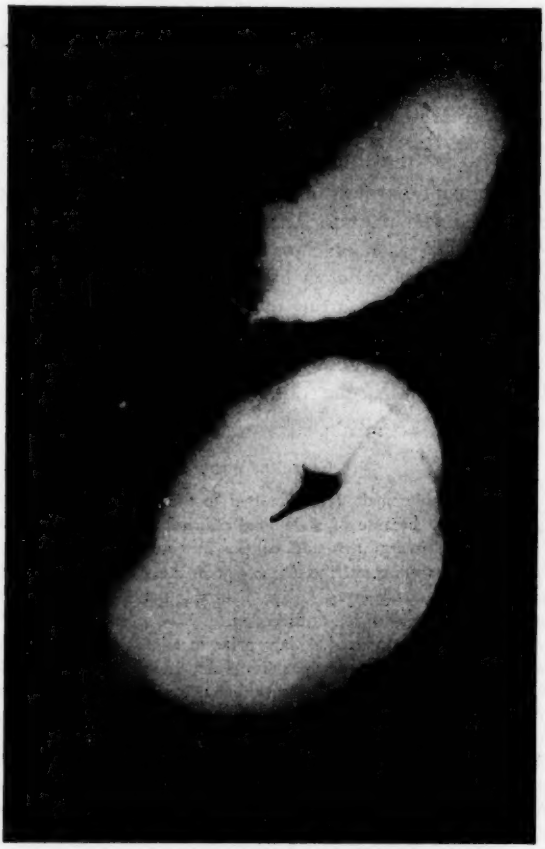

FIG. 1. Case 1. Barium enema. Note filling defect in region of right half of transverse colon suggestive of intussusception.

revealed "partial obstruction in the region of the hepatic flexure of the colon, probably due to intussusception."

Notwithstanding this finding, patient continued to have soft stools daily and neither abdominal nor rectal examination revealed the presence of a mass. Fractional small intestine study with 4, 6 and 8 hr. examinations verified the presence of intussusception causing a partial obstruction in what appeared to be the right half of the transverse colon.

Ten weeks after the onset of abdominal pain, a laparatomy was performed. Operative findings were:

"Malrotation of the colon, no ascending colon seen, the cecum was located in the right upper quadrant and passed directly to the transverse colon. The terminal 20 cm. of the ileum was markedly thickened and inflamed. The peritoneal cavity contained a serous reactive fluid indicative of chronic obstruction. The appendix was completely invaginated on itself and on opening the cecum it projected within the lumen as a polyp. The cecum inferior and lateral to the appendix was invaginated in the cecal cavity. The wall of the cecum was about 1.5 cm., thick, hard and fibrotic and covered with a shaggy exudate. The thickened ileum may have been due to an intussusception that had reduced itself. The cecum and transverse colon were mobile and could easily be delivered into the wound. With the cecum open the ileocecal valve was explored and found to be patent. The portions of the cecum that comprised both the intussusception and intussuscepiens were amputated. This included the appendiceal stump."

Postoperative course was uneventful and patient was discharged on the 15th postoperative day. A follow-up barium enema was done 2 mos. later and revealed a normal intestinal pattern. Patient has gained 3.2 kg.

Case 2. M.M., a 26 mo. old white male child, was admitted to the Pediatric Service of Queens General Hospital on May 8, 1948, with a history of intermittent colicky abdominal pain of 6 wks.' duration. The child would bend over and hold his abdomen. Anorexia and indefinite amount of weight loss were noted. There was no vomiting or diarrhea. Patient continued to have a dark brown bowel movement daily. Parents were advised by family physician to watch for worms or blood but none was ever noticed. Stools were never tarry.

Parents observed that while the child would be having pain, "moving bumps" would cross the abdomen. The remainder of the systemic history was negative. Developmental and past medical history was negative. No familial diseases were noted.

Physical examination revealed a well developed, somewhat pale white male, weighing 11.7 kg., in acute distress. The only positive findings were limited to the abdomen, which was soft, but abnormally large loops of intestine were palpable. Visible peristalsis was noted. No definite mass was palpated either abdominally or rectally and there was no blood on the examining finger.

Hemogram was within normal limits and there was no basophilic stippling. Urine showed a 3 plus acetone. Warm stool following a tap water enema did not reveal any ova or parasites. Benzidine test for occult blood was positive.

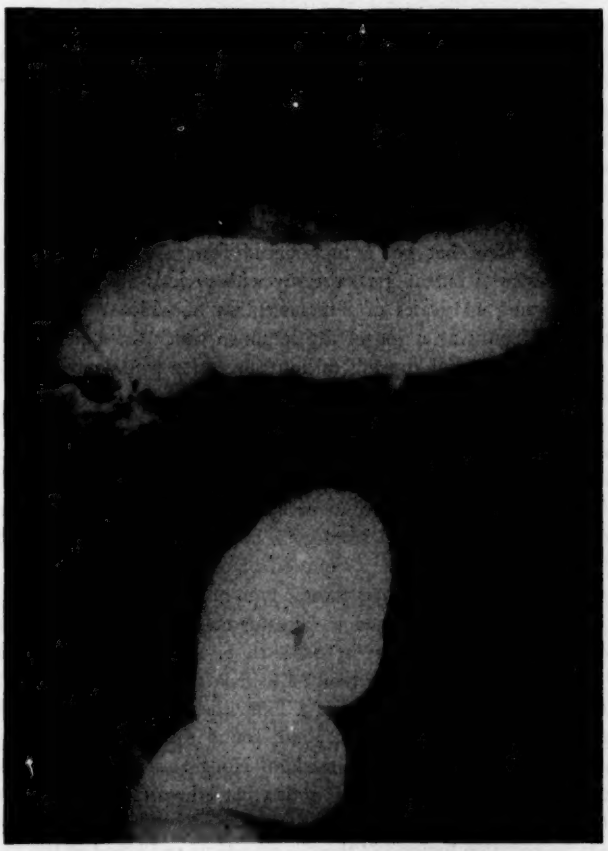

FIG. 2. Case 2. Barium enema. Ascending colon shows bizarre rarefied shadows apparently representing intussuscepiens containing invaginated small intestinal coils, intussusceptum.

Barium enema examination (see Fig. 2) "disclosed considerable gaseous distention and multiple fluid levels in the small intestinal coils consistent with mechanical obstruction. The opaque enema solution was seen to fill readily to successive portions of colon up to the hepatic flexure. The ascending colon shows bizarre rarefied shadows apparently representing an intussuscepiens containing invaginated small intestinal coils, the intussusceptum." Roentgenographic opinion was ileo-cecal intussusception.

Patient was immediately prepared for surgery and laparotomy was performed under open drip ether enesthesia.

An ileo-cecal intussusception was found extending to the hepatic flexure of the colon. The apex of the intussusception was an inverted Meckel's diverticulum which was located about 20 cm. from the ileo-cecal valve. This was resected and the ileum was closed by means of a primary end to end anastomosis.

Postoperatively, patient was placed on a modified Ochsner regime plus streptomycin for 4 days.

Course was uneventful except for a thrombophlebitis at a cut-down site which developed on the 4th postoperative day. This responded rapidly to penicillin and anticoagulant therapy and patient was discharged on the 12th postoperative day and referred to the pediatric clinic.

Comment

Garvie and Kemp,[1] reviewing chronic intussusception in children, found that the only reliable clinical feature is the history of repeated attacks characterized by sudden onset of gripping abdominal pain. All other signs of intussusception may be absent. They state that the tumor can be easily missed. It was impossible to palpate a tumor mass in either of the cases presented here. Still[2] notes that loss of weight is a prominent sign of chronic intussusception. In Case 1 there was marked evidence of malnutrition.

It is important to note that intussusception of the appendix is usually chronic in type. Fraser,[3] reviewing 82 cases of appendiceal intussusception, concluded (a) that the condition is seen most commonly in children, and (b) that the symptoms average several months in duration. The symptoms consist of mid-abdominal colic, loss of weight with vomiting (usually present but not a pronounced feature). Only a few cases display melena. The colic is brief but of great severity with periods of complete freedom from pain. Kahle,[4] analyzing 151 cases of intussusception of which 71% were in children, had only one case of intussusception of the cecum in which the appendix was involved. He makes a point that "partial appendiceal intussusception is undoubtedly more frequent than the cases reported in the literature would seem to indicate." Mayo and Phillips,[5] in a study of 39 cases of chronic intussusception, report four cases of appendiceal intussusception with no deaths. Their youngest patient with any type of chronic intussusception was 10 years old.

The case of intussusception due to an invaginated Meckel's diverticulum is unusual primarily because of the 6 weeks' history of symptoms prior to hospitalization and operation. Most authors[6–10] mention a duration of one to four days which makes these cases conform to the acute rather than chronic type of intussusception.

Harkins,[6] in a study of 160 cases in intussusception due to invaginated Meckel's diverticulum, found the average age at onset to be 13 years. The male:female ratio approximated 4:1. He cited a mortality of 74% in infants under 1 year of age, 56% in children under 5, and 36% in patients over 5. Fitzwilliams,[11] in a review of the pathology and etiology of 1000 cases of intussusception, found that 1.5% of all cases of intussusception are caused by Meckel's diverticulum. Hogg and Donovan[12] report Meckel's diverticulum in 4 of 123 cases. Jackson[13] states that "these cases that develop intestinal obstruction have the classical symptoms of this condition and are unlike intussusception in that there is no palpable tumor and there is no mucus and blood in the stools showing up after the other symptoms are in evidence."

Atwood[7] presents three mechanisms by which a Meckel's diverticulum may produce intestinal obstruction: (1) The obliterated omphalo-mesenteric duct in the form of a fibrous band may constrict the bowel. (2) The tip of the diverticulum may attach itself to some point in the peritoneal cavity and act as a band causing strangulation or volvulus. (3) The diverticulum may invaginate itself into the lumen of the bowel and start an intussusception. This last named mechanism was in evidence in the second case (M.M.) presented here.

Although vomiting is present in the vast majority of cases of intussusception due to an invaginated Meckel's diverticulum, this patient never vomited. Perhaps this might be explained by the fact that there was not complete obstruction.

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Spanish Abstract

Intususcepción Crónica

Se han presentado dos casos de intususcepción crónica. El intususceptum estaba formado en el Caso 1 por un apéndice invertido y en el Caso 2 por un divertículo Meckel invaginado.

Ambos de estos dos niños, varones, de 5 años y 26 meses respectivamente, fueron admitidos con historias de dolores abdominales intermitentes de varias semananas. El Caso 1 mostró sangre visible y oculta en las deposiciones a intervalos, pero las deposiciones eran por lo general suaves y ocurrían una vez al día, aunque había una pequeña diarrea o constipación a veces. No hubo ningún cambio en la costumbre del intestino en Caso 2, aunque se encontró sangre oculta en la deposición. Los vómitos, completamente ausentes en Caso 2, eran un signo pequeño en Caso 1. El examen del recto fué negativa en ambos casos. En ambos casos se confirmó la diagnosis de obstrucción intestinal parcial hasta después de hacer estudios Roentgen con una sustancia opaca.

Aunque ambos niños mostraron anorexia y pérdida de peso, el síntoma clínico sobresaliente fué el dolor abdominal cólico intermitente. Por consiguiente, se aconseja que la intususcepción crónica sea considerada en la diagnosis diferencial de todos los casos de dolores abdominales cólicos persistentes, aún cuando no haya prueba de obstrucción.

88-03 146th Street

PENICILLIN THERAPY OF DIPHTHERIA CARRIERS

An Analysis of 70 Cases

By JEROME T. Y. SHEN, M.D.
St. Louis, Mo.

INTRODUCTION

THE diphtheria carrier problem is particularly important in regard to children because of the following facts: 1. High incidence of diphtheria cases, mortality and susceptibility in children. 2. Peculiarity of the anatomy of the throat and nasal passages in children favoring the establishment and maintenance of the carrier state. 3. Technical difficulty in treating children because of their lack of cooperation.

The incidence of diphtheria carriers is low without epidemics, but rises rapidly when epidemics occur.[1, 2] In spite of the dramatic drop of the incidence of diphtheria cases in this country, there is a definite increase of the carrier rate in New York City and in the State of Ohio.* The highest incidence occurred among the age group between 5 and 14.

A diphtheria carrier is a person who is immune to diphtheria infection but harbors the virulent diphtheria organisms. The diagnosis of diphtheria carrier state is established by the isolation of the virulent bacilli and a negative Schick skin test. Diphtheria carriers can be classified by chronicity into transient and chronic; by the way of getting the infection, into contact and convalescent; by anatomic distribution, into throat, nasal, aural, etc., and by the types of C. diphtheriae, into gravis, intermedius and mitis.

NONPENICILLIN THERAPY OF DIPHTHERIA CARRIERS

Numerous different methods have been tried to cure diphtheria carriers without uniformly successful results. The following are the methods used, arranged in a more or less chronologic manner:

1. Local antiseptics—Almost every kind of antiseptic (mercurochrome,[4] gentian violet,[5] etc.) has been tried. The success of any local therapy depends on the close and rather constant contact of the drug with the organisms. It will not be effective in those patients who harbor the bacteria in deep crypts or submucosa of the nasopharyngeal tissue.

2. Local bacterial sprays[6, 7]—The purpose of this method is to overgrow C. diphtheriae by some other bacterial flora. Staphylococcus aureus, Lactobacillus and Bacterium coli have been used without permanent benefit. The method has been abandoned entirely because of its potentially harmful result.

3. Surgical correction of nose and throat conditions.[8-10]—This is usually the only way to remove those chronic foci which cannot be reached by drugs locally or parenterally. Excellent results have been reported, especially in the use of tonsillectomy.

From the Department of Contagious Diseases, City Hospital of St. Louis, Mo., and the Department of Pediatrics, St. Louis University School of Medicine, St. Louis, Mo.

(Received for publication Nov. 30, 1948.)

* In New York City, for children under 15 years of age, the average yearly diphtheria carrier rate (per 100,000 population) was 12.5 from 1942 to 1944 and 19.1 from 1945 to 1947. In the State of Ohio, the corresponding rates for all ages were 0.7 and 1.4.[3]

4. Irradiation[11-13]—Roentgen treatment has been used mostly because of its shrinking effect on the lymphoid tissue and its clearance of the secondary infection. Although it is harmless, its use should be reserved for selected cases. Ultraviolet ray has been tried without encouraging results.

5. Vaccine[14, 15]—The rationale of using vaccine made of killed C. diphtheriae is to increase or mobilize the antibacterial titer in the blood. Results have not been satisfactory, probably due to the following facts: (a) Diphtheria endotoxin is a poor antigen, so that antibacterial immunity is transient and difficult to establish; (b) The most deeply seated bacteria in carriers are not readily attacked by the antibodies produced.

6. Sulfanilimide group of drugs—It is not used any more because C. diphtheriae is not sensitive to the drug.

Penicillin Therapy of Diphtheria Carriers

Review of Literature

C. diphtheriae is considered to be quite sensitive to penicillin, although certain resistant strains have been isolated. With proper dosage, penicillin has been recovered in the saliva of animals and high concentration has been found in the buccal mucosa.[16]

In 1943, Herell and Kennedy[17] reported what was probably the first case of a diphtheria carrier treated by penicillin. The patient was a convalescent carrier eight years of age. He had received antitoxin and had had a tonsillectomy performed. He had been given 160,000 units of penicillin by the continuous intravenous method over a period of four days. Therefore, whether or not the cure was due to penicillin cannot definitely be stated.

Berman and Spitz[18] reported the cure of 10 cases of carriers with only five days of local penicillin treatment by nose drop and throat spray. Seven of the untreated cases cleared up spontaneously within five weeks, but five others remained positive for six to seven weeks. These five became negative after five days of local treatment. Among the 22 cases, 12 showed positive virulence tests. Skinner[19] reported 28 cases of clinical diphtheria and virulent carriers treated with intramuscular penicillin with definite benefit. He thought that 100,000 units per day should be given and cases not responsive to small doses cleared up by this larger dose.

Kocher and Siemsen,[20] in 1946, presented a report of a total failure in nine convalescent carriers treated by intramuscular penicillin, using 24,000 units every three hours for seven days. However, in 74% (23 cases) of the 31 carriers treated by lozenges and sprays, cultures became consistently negative from the first to the tenth day after therapy. Although five consecutive negative cultures were required to release the patient, most of the negative cultures in this series were taken when the patients were still on treatment. Twenty-six per cent (eight cases) of the cases of this study remained as carriers in spite of the local therapy and they were found to have large, cryptic tonsils. Tonsillectomies were performed on all of them and all cleared up without further treatment, except one, who needed eight days of penicillin application. There was one case not responsive to lozenges for 13 days, but it cleared up promptly after nasal spray. One case had a positive nasal culture after tonsillectomy. In the same year, Paul and his associates[21] failed to cure diphtheria carriers by having the patients inhale nebulized penicillin solution through the nose and exhale through the mouth, and vice versa. The solution contained penicillin 2,000 u./cc. of 10% glycerine in normal saline. It was inhaled for 15 minutes using 2½ cc. four times a day. The same negative result was obtained by using 100% oxygen instead of air. The authors thought that higher concentration and a less minute

droplet type of spray might possibly be more effective. Davison[22] treated a case of exudative tonsillitis with positive virulent diphtheria culture by 1,000,000 u. of penicillin with the final disappearance of the organism.

Weinstein[23] in 1947 studied 10 controlled and 13 penicillin-treated cases of virulent diphtheria carriers. Five of the 10 controlled cases became negative within a period between the 10th and the 52nd day. Two were discharged 54 days after admission still with positive cultures. Two remained as carriers even after tonsillectomies were performed 90 days after admission. Nothing was mentioned about the 10th case in this group. In the 13 penicillin-treated cases the time required to clear up the infection was between 2 and 32 days. All these cases had been followed for one to three weeks after the first negative culture. Two carriers cleared up after the second course of intensive therapy. A dose of penicillin 240,000 u. per day for 12 days eradicated the bacteria in three to four days; therefore, the author suggested that this should be the minimum dosage for chronic carriers. In the same paper, marked reduction of the duration of convalescence in clinical diphtheria by large doses of penicillin was noticed. Magnol and Igleslas[24] found encouraging results by local penicillin treatment in seven cases of carriers. Peterson,[25] however, was of the opinion that no definite conclusion could be drawn about the penicillin therapy in carriers, since not enough cases had been on record.

Karelitz and his associates[26] treated 35 virulent convalescent carriers with penicillin locally, intramuscularly, and by the combination of the two methods. Nose drops and sprays were used in eight cases. All ceased to be carriers within seven days. Two of another 13 carriers also cleared up after 7 and 11 days of local treatment, respectively. However, 11 of them remained as carriers after therapy was discontinued. Twenty thousand u. of penicillin given intramuscularly every three hours terminated the carrier state within four days in nine of the 14 cases so treated. Two cases cleared up after 12 days of treatment, one became positive again after the second course of penicillin, one failed to respond after 2,000,000 u. given in 12½ days and in one case the infection cleared up by nasal sprays after recurrence. The criterion for release of the patients in this study was nine consecutive negative throat cultures within a period of 18 days. Of this series, 83.3% had tonsils which were large, cryptic, irregular, and in many cases, scarred. The authors believed that there seemed to be a clinical correlation between the persistence of the carrier state and the character of the tonsillar tissue present. The patients most difficult to clear up were those with large and cryptic tonsils.

Recently Levy[27] reported success in treating three virulent pharyngeal carriers by lozenges and one virulent nasopharyngeal carrier by penicillin spray. Negative cultures were obtained immediately after, one week after, and six months after discontinuation of penicillin, respectively. The author believed that for acute diphtheria cases, as well as carriers, parenteral penicillin was of little value. Wszelaki and his associates,[28] however, highly recommended the use of penicillin in all clinical diphtheria by the parenteral route.

This study presents a series of 70 cases of diphtheria carriers treated with penicillin in the City Hospital of St. Louis, Mo.

Material and Method of Study

All cases were patients with at least 1 positive virulent nose and throat culture for C. diphtheriae admitted to the Department of Contagious Diseases of the City Hospital of St. Louis from April 1, 1945 to Sept., 1948, inclusive. Routine Schick skin tests were done in most of the cases. For discharge, at least 3 consecutive negative cultures were required after the drug was discontinued,

these to be taken not less than 24 hrs. apart. Antitoxin was used in those cases suspicious of mild acute diphtheria.

Penicillin dosage. Local nose and throat spray: 1,000 u./cc. every 3 or 4 hrs. Intramuscular penicillin: average dose for those below 1 yr. of age was 15,000 u. every 3 hrs.; for those between 1 and 13 yrs. of age, 25,000 u.; and for those over 13 yrs. of age, 30,000 u. Intramuscular procaine penicillin (Duracillin): ½ to 1 cm. daily, according to age. Four cases treated by massive doses of penicillin 10,000 u./lb. body wt./day, divided into 3 hr. doses.

Penicillin levels in blood and saliva before and after treatment were determined in 4 cases treated with massive doses of penicillin. In these cases the sensitivity of the organisms toward penicillin was also tested.

Analysis of 70 Cases

1. Yearly incidence of diphtheria carriers:

April, 1945-March, 1946	4
April, 1946-March, 1947	21
April, 1947-March, 1948	37
Total	62*

2. Sex incidence: Male 37 Female 33 Total 70
3. Race incidence: White 50 Negro 20 Total 70
4. Season incidence:

Yr.	Jan.	Feb.	March	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
1946	1	1	2	1	0	0	0	0	0	1	7	3
1947	3	2	4	3	1	0	1	1	0	10	3	1

5. Age incidence and its relation to Schick test:

Age of Patient	Total Cases	Schick Positive	Schick Negative	Non-recorded	Question-able
Below 6 mos.	3	0	0	3	0
6 mos.—1 yr.	1	0	0	1	0
1 yr.—2 yrs.	1	0	1	0	0
2 yrs.—4 yrs.	7	2	4	1	0
5 yrs.—9 yrs.	24	2	17	5	0
10 yrs.—14 yrs.	21	0	15	4	2
15 yrs.—19 yrs.	5	0	4	1	0
20 yrs.—39 yrs.	5	0	4	1	0
40 yrs.—59 yrs.	3	0	2	1	0
Over 60 yrs.	0	0	0	0	0
Total Number of Cases	70	4	47	17	2
Percentage	100	5.7	67	24.3	3

6. Incidence of previous immunization:

Immunization	No. Cases	Percentage
None	16	22.9
Nonrecorded	22	31.4
Primary shots without booster	7	10.0
Complete	16	22.9
Questionable	9	12.8
Total	70	100.0

7. Incidence of history of contact:

Condition of contact	From Clinical Cases	From Carriers	Total
Family contact	36	6	42
Nonfamily contact	11	0	11
No contact history			7
Convalescent carriers			2
Nonrecorded			8
Total			70

* Eight carriers admitted between April and September, 1948, inclusive, when added, make a total of 70 cases.

8. Condition of tonsils and average clearing time:*

Condition of tonsils	No. Cases	Percentage	Average C.T. (days)
Enlarged, cryptic	9	12.9	16.4 (2)†
Enlarged	35	50.0	6.4 (5)
Normal	19	27.1	5.6 (6)
Removed (tonsillectomy)	6	8.6	6.5 (2)
Nonrecorded	1	1.4	5.0 (0)
Total	70	100.0	7.5 (15)

9. C. T. and condition of tonsils in carriers with different forms of penicillin therapy:

a. Intramuscular penicillin:

Total No. Cases	Condition of Tonsils	Average C.T.
41	Enlarged 29 (70.7%)	8.3 days (5)†
	Normal 10 (24.4%)	
	Nonrecorded 2 (4.9%)	

If 3 cases of large and cryptic tonsils with a C.T. of 23, 26 and 37 days, respectively, were excluded, the average C.T. in this group would have been 4.9 days (5)

b. Intramuscular penicillin and nose and throat sprays:

Total No. Cases	Condition of Tonsils	Average C.T.
11	Enlarged 8 (72.7%)	6.3 days (3)
	Normal 3 (27.3%)	

c. Intramuscular procaine penicillin (Duracillin):

Total No. Cases	Condition of Tonsils	Average C.T.
9	Enlarged 5 (55.6%)	4.0 days (1)
	Normal 4 (44.4%)	

d. Nose and throat sprays alone:

Total No. Cases	Condition of Tonsils	Average C.T.
5	Enlarged 3 (60%)	7.0 days (2)
	Normal 2 (40%)	

e. Massive doses of penicillin: 4 cases in this group will be discussed later.

10. Analysis of 15 cases with C. T. over 5 days:

a. Incidence of normal throats in 2 groups of carriers:

Cases with C. T. over 5 Days:	Cases with C. T. less than 5 Days:
Total No. Cases 15	Total No. Cases 55
Cases with Normal Throat 3 (20%)	Cases with Normal Throat 21 (38.2%)

b. Age incidence:

Total No. Cases 15

5 yrs. (1 case), 6 yrs. (2), 7 yrs. (1), 8 yrs. (1), 9 yrs. (2), 12 yrs. (3), 13 yrs. (3), 17 yrs. (1), 34 yrs. (1).

c. Sex incidence:

Total No. Cases 15 Male 7 (46.7%) Female 8 (53.3%)

d. Relative study of the degree of inflammation of the tonsils:

	Total Cases	Cases with Inflamed Tonsils
C.T. less than 5 Days	55	18 (32.7%)
C.T. more than 5 Days	15	10 (66.6%)

11. Study of 4 cases with massive penicillin therapy:

a. In 3 strains of C. diphtheriae tested, 1 was sensitive to less than 0.1 u./cc. of penicillin and 2 to 0.1 to 0.4 u./cc.

b. Blood penicillin levels rose from nil to 0.1 — 1.0 u./cc. after therapy, while saliva levels rose from nil to less than 0.1 u./cc. except in 1 case where there was no level detected even after

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* Clearing time is defined here as the time between the beginning of treatment and the 1st negative nose and throat culture. For the sake of convenience, the abbreviation C.T. is used in this paper.

† The numericals in the parentheses indicate the number of the carriers from whom no positive culture was obtained during their stay in hospital. These cases were not counted in the calculation of the average C.T.

treatment. Blood and saliva specimens were all taken 1½ hrs. after injections. First portions of the saliva were discarded.

c. Two cases with 3 and 4 days of penicillin therapy, respectively, were readmitted with positive cultures 1 wk. after the 1st discharge. One of them had moderately enlarged tonsils and the other had apparently small ones. The former had a tonsillectomy performed after 1 day of penicillin treatment after readmission. Sections showed scarred cryptic tonsils with calcium deposits. Cultures taken 1 wk. after redischarge from both cases were negative.

12. Reactions local or general from penicillin—none.

Discussion

Similar to the reports of others,[29-33] in this series of 70 diphtheria carriers, the carrier state occurred in the following manner:

a. Essentially equal among the male and the female.
b. Two and one-half times more frequent in white than in the Negro people.
c. More frequently in autumn and winter.
d. Most frequently in the age group between 5 and 14.
e. Usually through the contact with a clinical case in the family.

The four Schick positive cases in this series were probably mild clinical ones.

Among the 70 cases, 62.9% had enlarged tonsils and 27.1% had normal ones. Pathologic sections of the specimens removed by tonsillectomy from some of the cases in the normal tonsil group showed cryptic tonsils. This simply demonstrates the fact that clinical appearance of the tonsils, especially by the usual oral examination, is unreliable. The high incidence of throat pathology in carriers has been repeatedly proved.[34, 35]

In this study 30,000 u. of penicillin, given intramuscularly, every three hours seems to be effective in getting three daily consecutive negative cultures after discontinuation of the therapy. The average C.T. was 4.9 days.* It is unfortunate that check-up cultures after discharge were not taken, although no return case was encountered.

The average C.T. for those treated with both intramuscular and local penicillin was 6.3 days.

In the 11 cases treated with procaine penicillin (Duracillin), the average C.T. was 4.0 days. Although the incidence of enlarged tonsils in this group was lower than that of the other groups (55.6% as compared to 70.7% in the intramuscular group and 72.7% in the combined intramuscular and local group), the good result could be due to the larger dosage and more sustained level of the procaine penicillin. However, this series was too small to yield any significant conclusion.

Local treatment alone gave a C.T. of 7.0 days. Since there were only five such cases treated, no definite comment can be made.

In this series the average C.T. for those with normal, enlarged and enlarged cryptic tonsils was 5.6, 6.4, and 16.4 days, respectively.

Carriers with a C.T. of more than five days showed a much lower percentage of normal sized tonsils and a much higher percentage of inflammation than the group with a C.T. of less than five days.

The above results point out that there is a definite relationship between the incidence and degree of the throat pathology and the response to penicillin treatment.

Results of the study of the four cases treated with massive doses of penicillin suggest

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* Three cases of large and cryptic tonsils, with a C.T. of 23, 26, and 37 days, respectively, were excluded in the calculation of the average C.T.

that no amount of the drug can attack organisms protected by chronic fibrotic crypts. Penicillin, likewise, has no value in preventing reinfection.

Conclusions

In simple cases of diphtheria carriers intramuscular penicillin is highly effective. Five thousand units per pound of body weight per day for five days seems to be curative. Procaine penicillin is preferable because of its convenience of administration and its more sustained level. Local sprays or nose drops can be employed along with parenteral therapy whenever their use is practical. A solution with 10,000 units per cubic centimeter is recommended.

All carriers should have a thorough nose and throat examination by an otolaryngologist. Serious nose or throat pathology should be corrected surgically after one or two days of penicillin administration. Mild pathology should also be corrected surgically with the administration of penicillin in cases where the infection refuses to clear up or recurs after discharge.

In cases that have recurred without any nose or throat pathology, a sensitivity test of the organism should be done and the dosage of penicillin adjusted. If the organisms are resistant to penicillin, other methods previously discussed (under "Nonpenicillin Therapy") should be tried.

Two consecutive daily negative nose and throat cultures are believed to be necessary for discharge. A separate nose and throat culture should be taken one week after discharge for check-up purposes.

Summary

The diphtheria carrier problem and its importance in children is discussed. Nonpenicillin therapy of diphtheria carriers is briefly reviewed and commented upon. Literature on penicillin therapy in the diphtheria carriers is reviewed.

An analysis of the results of 70 cases of diphtheria carriers treated by different forms of penicillin therapy is presented and commented upon, especially in regard to the correlation between the effectiveness of the therapy and the pathology of the nose and throat. Rational treatment of diphtheria carriers is suggested in the conclusion of the paper.

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SPANISH ABSTRACT

Terapia de Portadores de Difteria con Penicilina
Análisis de Setenta Casos

El autor discute el problema del portador de difteria, su importancia en los niños, y revisa la terapia de dichos portadores antes del uso de la penicilina y ahora con el uso de penicilina en varias formas. Se presenta un análisis de setenta casos de portadores de difteria tratados con penicilina, y se discute la efectividad de dicho tratamiento con relación al grado de patología presente en la nariz y garganta.

En casos simples de portadores de difteria, penicilina intramuscular es muy efectiva. Cincuenta mil unidades por libra de peso por día por cinco dias parece ser suficiente. Se prefiere la penicilina con procaína por razón de la facilidad de administración así como la concentración que se obtiene en la sangre. Aplicaciones locales en la nariz y garganta con soluciones de 10,000 unidades por centímetro cúbico se recomiendan para suplementar la terapia parentérica.

Cada portador de difteria debe tener un examen complete de nariz y garganta por un otolaringólogo, y toda patología seria debe corregirse quirúrgicamenta después de uno o dos días de tratamiento con penicilina. Casos con patología menor en cuales la infección no desaparece o recurre después de tratamiento deben ser sujetados a cirugía en la nariz o garganta.

En aquellos casos que recaen sin patología en nariz o garganta, el organismo se debe probar con una reacción de sensitividad y la dosificación de la penicilina debe cambiarse de acuerdo. Si el organismo se encuentra resistente a la penicilina, otros métodos se discuten en el árticulo para combatir tal eventualidad.

Dos cultivos negativos de nariz y garganta en días consecutivos se usa como criterio para considerar a la persona curada. Una semana después, debe obtenerse otro cultivo para confirmar la efectividad del tratamiento.

634 North Grand Boulevard

EMBRYOMA OF KIDNEY (WILMS' TUMOR) IN CHILDREN

By LLOYD B. DICKEY, M.D., AND L. R. CHANDLER, M.D.
San Francisco, Calif.

APPROXIMATELY 2% of deaths from cancer occur in people under 20 years of age,[1] which refutes a common impression that childhood cancer is rare. The prognosis of cancer in children is poor, but this is partly so because the time is often longer than it need be between the onset of symptoms, and the recognition of the true condition and its proper treatment.

Embryoma of the kidney, usually known as Wilms' tumor after its original description by this author,[2] is a common abdominal malignancy in infants and small children. Because it may be amenable to early treatment, it is important that every physician know of its existence and be on the alert for symptoms that lead to its early recognition.

A series of 12 cases, in all of which the diagnosis of embryoma of the kidney was confirmed by biopsy or necropsy, is presented here.

CASE MATERIAL

Six of the 12 patients were male and 6 female. In the reported cases in the literature, the sex distribution is about equal. The great majority of cases are observed in the first 3 yrs. of life, and are rarely observed after 7 yrs. The age at onset in 3 of these cases was between 5 and 6 mos.; in 5, it was between 1 and 2 yrs., and 4 of the children were over 3 but under 7 yrs. of age. Moore[3] observed the lesion in a man of 56 yrs., and Silver[4] in a man of 27. The latter also observed a case in a male infant of 3 days of age.

In these 12 cases, 4 received no breast milk whatever, 2 were breast-fed entirely for 1 yr., and 1 was breast-fed for 1 mo. only. The type of feeding was not noted in 5.

An abdominal mass was the 1st symptom in 10 of the cases. In 2 of these, both 16 mos. of age, the mass was found on routine physical examination by the physician in a well-baby clinic, the parents being unaware in both instances of the presence of the tumor. One of these is now living 15 yrs. later. It was impossible to persuade the parents of the other infant to agree to operation until 2 wks. later. He survived only 4 mos.

Abdominal pain was the initial symptom in the other 2 cases, 1 of which was diagnosed preoperatively as an appendiceal abscess. The tumor was regarded as inoperable. Biopsy material was diagnosed Wilms' tumor and this patient is living 8 yrs. after radiation of the tumor without removal. Other symptoms noted, but not initially, were loss of appetite in 3, loss of weight in 2, fretfulness in 2, and diarrhea, nausea and vomiting, regurgitation, and frequency and dysuria in 1 instance each. Hematuria was not observed. Pain, fever, and hematuria occurred less frequently in this series than in the reported cases.

Duration of the symptoms from discovery to initial treatment in these 12 cases varied from 10 days to 3 mos., and bore no apparent relation to ultimate prognosis.

Physical findings were chiefly those associated with a large mass in the abdomen. Masses varied in size from about 7 x 5 cm. to about 18 x 10 cm. Six were on the left side, 6 on the right. The patient with the smallest mass and the one with the largest both recovered. One patient had a right nephrectomy at 5½ mos. of age, and a similar tumor was detected on the left side less than 10 mos. later. One patient had an umbilical hernia through which the tumor was first felt by the parents. One was poorly nourished and another emaciated when first seen and both of these died.

From the Departments of Pediatrics and Surgery, Stanford University School of Medicine, San Francisco, Calif.

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Laboratory findings were not helpful. Sedimentation rates varied between 1 mm. and 25 mm./hr. (Cutler), and there was no correlation between these rates and the outcome. Four had hemoglobin below 10.4 gm. %, but bore no relation to outcome. In 1, the white cells numbered 22,400 with polymorphonuclears 48%, in another 17,000 with polymorphonuclears 71%, both patients being among those who survived. The patient who died without operation had hemolytic streptococci and Staphylococcus aureus in the urine.

Urograms of all patients so studied showed deformities or a nonfunctioning kidney on the side of the tumor, with 1 exception. In the 1 patient showing no deformity (E.M.), the kidney was not involved. It is interesting to note that of the 3 showing calcifications of the tumor, all are living.

Treatment

The tumor, with the kidney of that side, was removed in 9, and the tumor only, in 1. Three of these patients are alive and well. In the patient in whom the tumor only was removed, a low right rectus incision was made. Exploration revealed a retroperitoneal tumor more than 5 cm. in diameter, roughly spherical in shape, lying well below the right kidney and displacing the right ureter anteriorly. The posterior peritoneum was incised lateral to the cecum and the tumor mobilized without much difficulty except for rather firm adhesions to the right iliac vessels. The tumor was enucleated en masse. The incision in the posterior peritoneum was closed and the abdominal incision closed in layers without drainage. Microscopic examination by Dr. David A. Wood, Stanford University Hospital Department of Pathology, confirmed the diagnosis of adenomyosarcoma (Wilms' tumor). In 1 patient who died there was metastatic extension enough to demand resection of the descending colon. In a single instance the abdomen was opened and the condition considered inoperable. Biopsy was diagnosed Wilms' tumor. The patient was given roentgen treatment at once, and is alive and well 8 yrs. later. One had radiation without operation, and did not survive. Autopsy confirmed the diagnosis of Wilms' tumor.

Of the 10 in whom the tumor was removed, 3 had preoperative radiation only, and 2 are living and well. Those having postoperative radiation only were 4 in number: 1 is still living and well and 3 are dead. One patient had both preoperative and postoperative radiation, and 2 had no radiation; all 3 died later.

Radiation was given at 200 kv., hvl. 1 mm.Cu, 100 to 150 r a day, crossfiring to 1100 to 2000 r in skin of each area. The 4 who survived received the smaller preoperative doses and middling postoperative doses.

All 4 patients now living and well have had recent skeletal and pulmonary roentgen surveys, and all are free of signs of metastases.

These figures leave a survival rate of 4 out of 12 cases, or 33.3%, which is excellent for any kind of abdominal malignancy. In 1941, Ladd and White[5] summarized recorded cases on this subject up to that time, and out of 563 cases found 38 cures. Their own series consisted of 14 cures out of 60 operated cases, or a survival rate of 23.3%. Weisel, Dockerty, and Priestly[6] reported 7 cures out of 42 patients who had nephrectomies. Nesbit and Adams[7] reported 58.4% cured after operation, or 7 out of 12 patients. In Dean's series,[8] there were 20 patients treated only with radiation, of whom 5 were still alive after 5 yrs. Silver,[4] in a series of 18 cases, had 10 survivals, or a rate of 55.5%. Of the 18 cases, 13 had a nephrectomy, which, with 10 survivals, gives a rate of 76.9%, an enviable record.

Comment

The most important single items in the early diagnosis of Wilms' tumor are the alertness of the physician and the keenness of the powers of observation of the parents. In most cases the presence of the tumor is the first and often the only symptom. This stresses the need for more than a casual examination in well-baby clinics and in physicians' offices of infants brought in chiefly for feeding advice. It suggests the advantage of extending the routine examination into the age group between the well-baby clinic and the child of school age. Only by stressing the importance of physicial examination of small children, if for no other reason at all, will the survival percentage rise in the case of operation for Wilms' tumor.

The usual laboratory procedures are not particularly helpful, although an increased

sedimentation rate, in the absence of some obvious explanation, should arouse suspicion of malignancy, even in infancy. A normal rate does not rule out malignancy. Urograms should always be done for the location of the tumor, to ascertain the condition of the other kidney, and for the differential diagnosis.

Immediate operation and removal should be the treatment of choice. According to Ladd and Gross[9]: "Preoperative irradiation implies that there must be a deferment of operation for several weeks to gain the optimum effects of the X-rays. During this time the tumor may begin to seed the blood stream and set up metastases, and the one chance for a permanent cure has been lost. Preoperative irradiation refutes one of the cardinal principles for treatment of these cases—namely, *removal of the mass as soon as it is discovered.*" Radiation, therefore, should be postoperative only, as time may be lost between the beginning of symptoms and removal. Any tumor that may be delivered through an abdominal or lumbar incision can be removed. In performing nephrectomy in infants and children, the transperitoneal approach is by far the most satisfactory. This tumor rarely metastasises early, but may infiltrate rapidly into adjacent abdominal organs, or invade the blood stream through the renal veins. Postoperative radiation is the logical adjunct to surgical treatment for attack on possible metastases. The other kidney may become involved independently. In the opinion of Ladd and Gross, "If a patient survives operation for a year and a half without evidence of recurrence, he can probably be regarded as a permanent cure."

Summary

A series of 12 cases of Wilms' tumor, in which the diagnosis was confirmed in all instances by examination of the gross or microscopic tissue, is reported, with a survival rate of 33.3%. Four patients are living and well, 4, 8, 10, and 15 years, respectively, after treatment. All recurrences appeared less than 10 months after treatment.

The sex incidence, and the sex survival incidence were exactly equal. Six tumors were in the left kidney, and six in the right.

Eight of the patients were under 2 years of age when first diagnosed and treated, and all were under 7 years.

The history of breast or bottle feeding was irrelevant.

In a large number of these and reported cases, the presence of the tumor was the first symptom, and in a considerable number the only symptom. This fact stresses the importance of careful physical examination of infants and young children, regardless of complaint, or of lack of it.

The finding of calcification in the tumor is possibly a good prognostic sign. All three patients in whom calcification was noted in the tumor are living and well.

Immediate removal of the tumor by transperitoneal nephrectomy, with postoperative radiation to the area, seems to be the advisable treatment.

Acknowledgment

Acknowledgment is made to Dr. Victor Richards and Dr. James Ownby for permission to include their two cases.

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SPANISH ABSTRACT

Embrioma del Riñón (Tumor de Wilm) en Niños

Una serie de doce casos de tumor de Wilms, en que el diagnóstico fue confirmado en todos los casos de exámenes de los tejidos gruesos ó microscópicos, es divulgado, el resultado fue en 33.3 por ciento de sobrevivientes. Cuatro pacientes están viviendo y bien, 4, 8, 10 y 15 áños después del tratamiento respectivamente. Todos los reparaciónes se presentan menos de diez meses después del tratamiento.

La incidencia del sexo y la incidencia de los sexos que sobreviven fueron exactamente iguales. Habia seis tumores n'el riñón del lado izquierdo, y seis n'el riñón del lado derecho.

Ocho de los casos eran menos de dos años de edad quando fueran diagnosticados y tratados, y todos eran menos de siete años.

La historia de alimentación al peche ó al botillita no es aplicable.

En muchos casos divulgados por nosotros y otros la presencia del tumor fue el primer síntoma, y en un numero considerable de casos fue el unico síntoma. Este hecho da mucha importancia á el diligente examen de los enfantes y de los miños, ya sea que haya que ja ó no.

El descubrimiento de petrificación en el tumor es posiblemente un signo útil en el prognostico. Los tres pacientes en que la petrificación fue descubrida en el tumor estan viviendos y sin enfermedad alguna.

Excisión del tumor immediatamente para nefrectomia trans peritoneal, con irradiacion post operativa en la ária, nos otros pensamos que es el tratamiento que debe ser seguido.

2351 Clay Street

NEW CONCEPTS OF THE ETIOLOGY, DIAGNOSIS AND TREATMENT OF CONGENITAL MEGACOLON (HIRSCHSPRUNG'S DISEASE)

By ORVAR SWENSON, M.D., EDWARD B. D. NEUHAUSER, M.D., AND LAWRENCE K. PICKETT, M.D.
Boston, Mass.

THE clinical syndrome now known as Hirschsprung's disease, or congenital megacolon, was recognized and described over 100 years ago.[1] A careful and complete description of two patients, including their clinical course and postmortem findings, was reported by Hirschsprung in 1886.[2] Since that time numerous publications have been issued regarding this syndrome and while there has been a general agreement in the clinical description and course of this disease, there has been considerable difference of opinion concerning the underlying pathology. Most observers agree that the Hirschsprung disease eponym should be reserved for those patients with hypertrophy and dilatation of the colon without mechanical obstruction. In this limited group of patients with congenital megacolon in which no mechanical obstruction can be demonstrated, the pathogenesis of the dilatation and hypertrophy has been debatable.

A study of 26 patients with congenital megacolon, made during the last five years at The Children's Hospital, has clarified to the authors the nature of this disease and a new treatment based on this concept has been instituted. There are certain clinical features of this disease that should be stressed because they support the authors' concept of the etiology of congenital megacolon. In all but one of the 26 patients, the onset of symptoms occurred in the first few weeks of life. In the remaining patient, the history was obscure as the child was adopted at six months of age and the early background was unknown. However, when the child was six months old, a diagnosis of congenital megacolon was made. Other reports on congenital megacolon have stressed the early onset of the disease. Both patients described by Hirschsprung[2] had symptoms beginning shortly after birth. Barrington-Ward[3] studied 19 patients with congenital megacolon in which the diagnosis was confirmed at autopsy. In 16 of these the inception was at birth. In the remaining three, constipation dated from two months, six months and 3½ years. One patient in this series was operated on during the first week of life. Dilatation and hypertrophy of the colon were found but no mechanical obstruction was present. All of this evidence suggests that the disease is congenital in origin. The marked preponderance of males reported in the literature is also evident in this series. In this group of 26 patients, only four were females.

A careful analysis of the histories and physical examinations of the group of patients reveals the whole clinical picture and course to be consistent with partial obstruction of the large bowel. All of the patients in this group had severe constipation and bouts of obstipation as the presenting complaints. In the periods of exacerbation of the disease,

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From the Surgical and Radiological Services of the Children's Hospital and the Departments of Surgery and Radiology of the Harvard Medical School, Boston, Mass.

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the children, particularly the older ones, complained of abdominal cramps and vomiting. Several mothers commented on the fact that audible gurgles could be heard emanating from the child's abdomen. The degree of abdominal distention also varied from time to time. In the children with distention it was possible to see the pattern of the dilated bowel through the thin abdominal wall and to observe peristalsis in the dilated colon. On palpation of the abdomen, large fecal impactions were frequently outlined, most commonly in the left lower quadrant. Despite these impactions in the colon, rectal examination demonstrated an empty ampulla in all patients except two. It is interesting that Hirschsprung[2] commented specifically on the absence of fecal material in the rectum, despite a large impaction in the colon. Thus it can be stated that the histories and physical findings in congenital megacolon are perfectly consistent with partial obstruction of the lower part of the colon, the severity of symptoms and signs being related to the degree of obstruction.

FIG. 1. Routine barium enema. Whole colon has been filled and abnormal area of rectosigmoid is obscured.

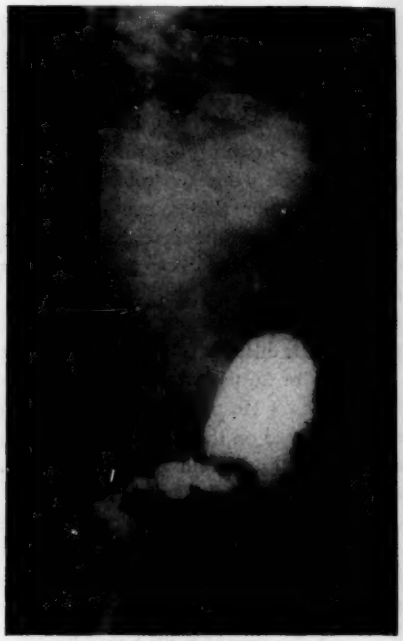

FIG. 2. Barium enema correctly performed which gives detailed outline of rectosigmoid and demonstrates narrowing in colon.

While the clinical picture has been consistent with partial mechanical obstruction, postmortem studies and findings in the operating room have never demonstrated any form of mechanical obstruction. However, it is well known that occasionally the clinical picture of megacolon can be produced by a true organic obstruction, such as a congenital web or stenosis of the sigmoid or anus. All the patients in this series were subjected to fluoroscopic examination of the colon during barium enema. Each presented the picture

of functional obstruction produced by a dyskinesia of the rectum or rectosigmoid and this could usually be detected only when the barium mixture was allowed to run slowly and in small quantities into the rectum. For satisfactory visualization of the rectosigmoid, it is essential to examine the patient in the oblique projection, because if this is not done the appearance produced is that which is so familiar in much of the literature—that of a colon which appears dilated to the anus (Fig. 1).

In these patients, a portion of the rectum or rectosigmoid, often a segment up to 10 cm. in length, was consistently less than normal in caliber. The contour was frequently irregular and often a turbulent and purposeless peristaltic activity could be seen. Occasionally there appeared to be reverse peristalsis, so that the barium mixture was carried cephalad into the sigmoid (Fig. 2). More often no peristaltic activity can be seen.

After this portion of the bowel was satisfactorily visualized, a small amount of barium was allowed to run through this area of abnormal function of the colon into the portion that exhibited dilatation. As soon as even a moderate amount of barium passed into the dilated portion of the bowel, it was usually no longer possible to see the area of dyskinesia as the markedly dilated and often redundant loop of sigmoid and proximal colon obscured the rectosigmoid completely.

This experience gave concrete evidence of a physiologic, partial obstruction of the rectum and rectosigmoid. If this conclusion was correct, colostomies above this point in the colon should give complete relief of the patient's symptoms.

Colostomies were performed in the normal bowel in three of the patients—that is, in the dilated portion of the colon—and in each instance all symptoms of Hirschsprung's disease disappeared. These patients behaved precisely as any patient would who had been relieved of large bowel obstruction by a colostomy. Closure of the colostomies was performed in these three patients and in each instance there was recurrence of the complaints which were not relieved until the colostomies were reopened. Colostomies have been performed on 12 other patients. Each one has been completely relieved of his symptoms and the large hypertrophied colon has decreased markedly in size.

The roentgen evidence of obstruction in conjunction with the clinical findings and experience with colostomies in these patients has led to the conclusion that the abnormality in Hirschsprung's disease rests exclusively in that portion of the rectum or rectosigmoid where the caliber of the bowel has been normal or less than normal but is the seat of a severe dysfunction, with disorganized peristalsis or failure of relaxation. The dilated and hypertrophied portion of the colon is believed to be simply the result of the longstanding partial obstruction. Therefore, it would seem that all therapeutic measures should be directed toward this short segment of malfunctioning bowel rather than to the obvious dilated and hypertrophied colon.

During the performance of transverse colostomies in the patients, the sigmoid loop was delivered in order to correlate the finding on direct examination of the sigmoid with what had been demonstrated in the roentgenograms. In all instances where the abnormal bowel extended up into the sigmoid, an abrupt change in diameter of the bowel was found. In some patients, the abnormal bowel was low in the pelvic cavity or below the pelvic peritoneum and, therefore, could not be seen. That such was the case could always be predicted from the roentgen films. Proximal to the point of narrowing, the colon would measure as much as 20 cm. in diameter. In the course of 5 cm., this tapered into bowel which was normal, or smaller than normal, in size (Fig. 3). In appearance and

to palpation, this bowel seemed far more normal than the dilated bowel above. However, the roentgen findings, as well as the experiences with colostomies in these patients, led to the conclusion that it was functionally deficient.

The next problem was to restore continuity of the intestinal tract so that the colostomy could be closed successfully. In most instances it was demonstrated by barium enema that the abnormal bowel extended down to the anus. Therefore, resection of the rectum would of necessity have to be performed down to the anus to assure removal of all of the malfunctioning bowel. No standard surgical procedure could be employed in this resection for none of them would leave the anus functionally intact.

FIG. 3. Photograph of sigmoid loop taken during performance of colostomy. Markedly dilated bowel is proximal sigmoid. This dilatation terminates abruptly in distal sigmoid and bowel becomes smaller in caliber than normal.

The usefulness of a special pull-through form of resection, which had been devised and tested in the laboratory, has been demonstrated in 23 patients.[4] This special type of resection, which preserves the anal sphincter, is performed as follows: A left paramedian suprapubic incision is made, extending from the symphysis to a point a few centimeters above the umbilicus (Fig. 4). The demarkation between the functionally inadequate bowel and the normal colon is evident by the abrupt change in diameter of the colon, or, if a colostomy had been performed previously, this point had been marked by several black sutures. This is important, for after a diverting colostomy the dilated bowel becomes normal and the point of transition from the functionally normal to abnormal bowel is indistinguishable by examination of the bowel. The resection is carried from above this point of change down to the anus.

The first part of the operation is the same as a combined abdominal-perineal resection. The sigmoid and rectum are freed from all attachments in the pelvis down to the levator

ani muscle. The bowel is then divided proximal to the abnormal portion and both ends are closed with continuous catgut sutures (Fig. 5). The distal end is then pulled out through the anus, and the mucosal surface, which is now presenting, and the perineum are prepared with Zephiran scrubs (Fig. 6). Drapes are placed and the bowel is opened transversely 2.5 cm. from the anal skin margin. The proximal bowel is pulled down through this opening (Fig. 7).

The anastomosis is made, using first a row of interrupted black silk Lembert sutures through the muscular coats of the two segments of bowel. Up to this point the procedure has been relatively aseptic. The proximal bowel is then opened and the mucosa of the two ends are approximated with interrupted chromic catgut sutures. The anastomosed bowel is then pushed back through the anus and the suture line assumes a position about 2½ cm. above the anal skin margin.

This operation has now been performed on 23 patients. There have been no deaths. In 15, preliminary colostomies had been performed because of the advanced state of the disease. Closure of the colostomy has been performed on all of these patients except two. Abdominal distention has disappeared. No special diets, laxatives of any form, or enemas have been used postoperatively and all of the patients now have normal bowel movements. As far as can be determined, they are normal children. Three infants, the youngest two months old, were subjected to this type of resection without preliminary colostomies. These youngsters were all operated upon before malnutrition had set in; they all tolerated a one-stage operation and have done well postoperatively.

Following operation, the children have an urge to defecate, which is reported by two of the older patients (8 and 9 years) to be normal, as far as can be determined from their descriptions. All of them have normal sphincter control, both as to performance and to findings on digital examination. Most of these patients have been followed only a few months. However, one has been followed one year and another for 10 months and both continue as normal children.

These children have had such satisfactory results following operation that barium enema studies have not been performed in all subjects. However, for purposes of clinical investigation follow-up roentgen studies were made on five of them. The colon remains slightly larger than normal in these children. However, the emptying is excellent (Fig. 8).

Discussion

As has been stated, a true organic stenosis of the anus or rectum may occasionally be encountered in a patient with the clinical picture of congenital megacolon, and such a lesion should be looked for in patients suspected of having Hirschsprung's disease. Reports have been made of patients in whom there was a segment of narrow bowel distal to the megacolon but no significance has been placed on these anatomic observations. During the past five years, 26 patients have been studied with clinical diagnosis of Hirschsprung's disease, and in each one it was possible by careful examination to demonstrate a spastic segment of colon in the rectum or rectosigmoid with dilated bowel proximal to this. If such an appearance can be disclosed in a patient with a clinical picture of Hirschsprung's disease, it is felt that excision of the malfunctioning distal portion of the bowel should be performed with preservation of the anal sphincter, providing medical therapy has been unsuccessful. Two patients in this group are being managed successfully on a medical regime with mecholyl bromide. There is a third patient in

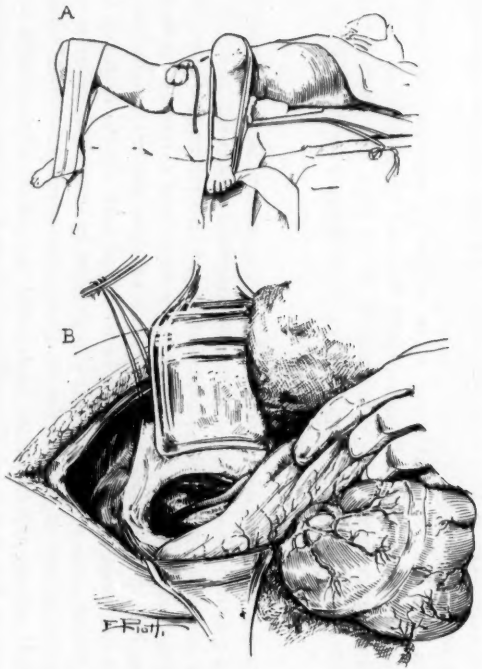

FIG. 4. A. Position on table is so arranged that 2 teams can work during 2nd half of operation. When pull-through is done, 1 team performs anastomosis; other team closes abdomen. B. Pelvis is exposed through midline incision. Right ureter has been identified.

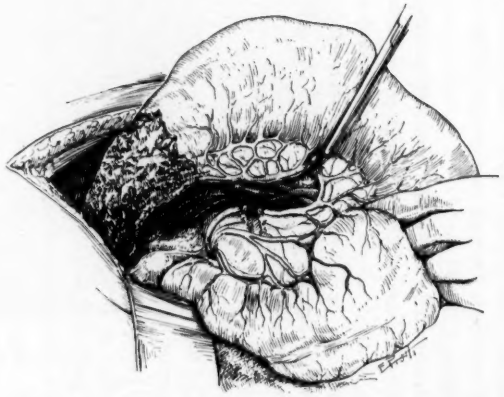

FIG. 5. Sigmoid loop has been delivered, rectosigmoid freed down to levator ani. Note change in caliber at peritoneal reflection in this patient. Sigmoid is now divided at about its midpoint.

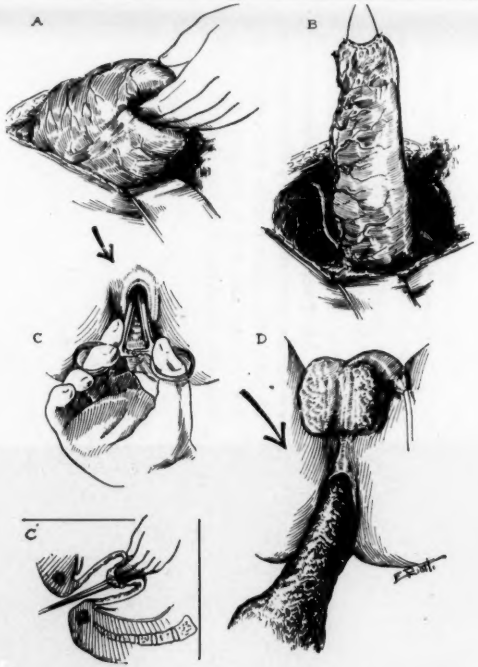

FIG. 6. A. Beginning of inversion of distal bowel is begun from above. B. Proximal colon is ready to be pulled through. C. Long curved clamp is inserted through anus. C.' Distal bowel is grasped and pulled through. D. Distal bowel protrudes from anus with its mucosa on surface.

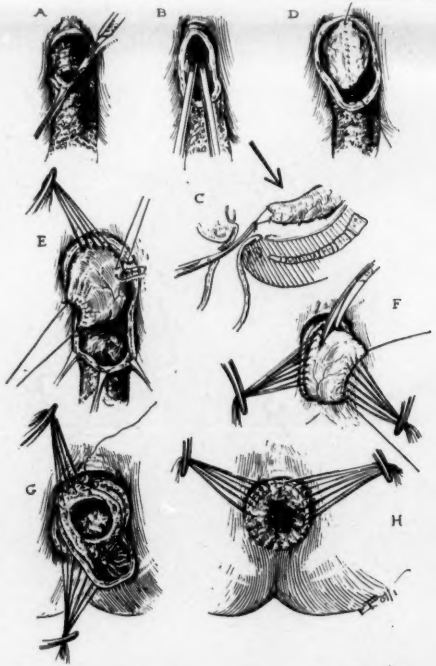

FIG. 7. A. Distal bowel is cut across 2.5 cm. from skin margin. B. Clamp is inserted through opening. C. Sutures on proximal bowel are grasped. D. Proximal bowel is pulled through distal bowel. E. Muscular surfaces are approximated by interrupted silk sutures. F. End is cut off proximal bowel. G. Mucosa is approximated with chromic catgut sutures. H. Suture line is completed and suture line is ready to be pushed through sphincter.

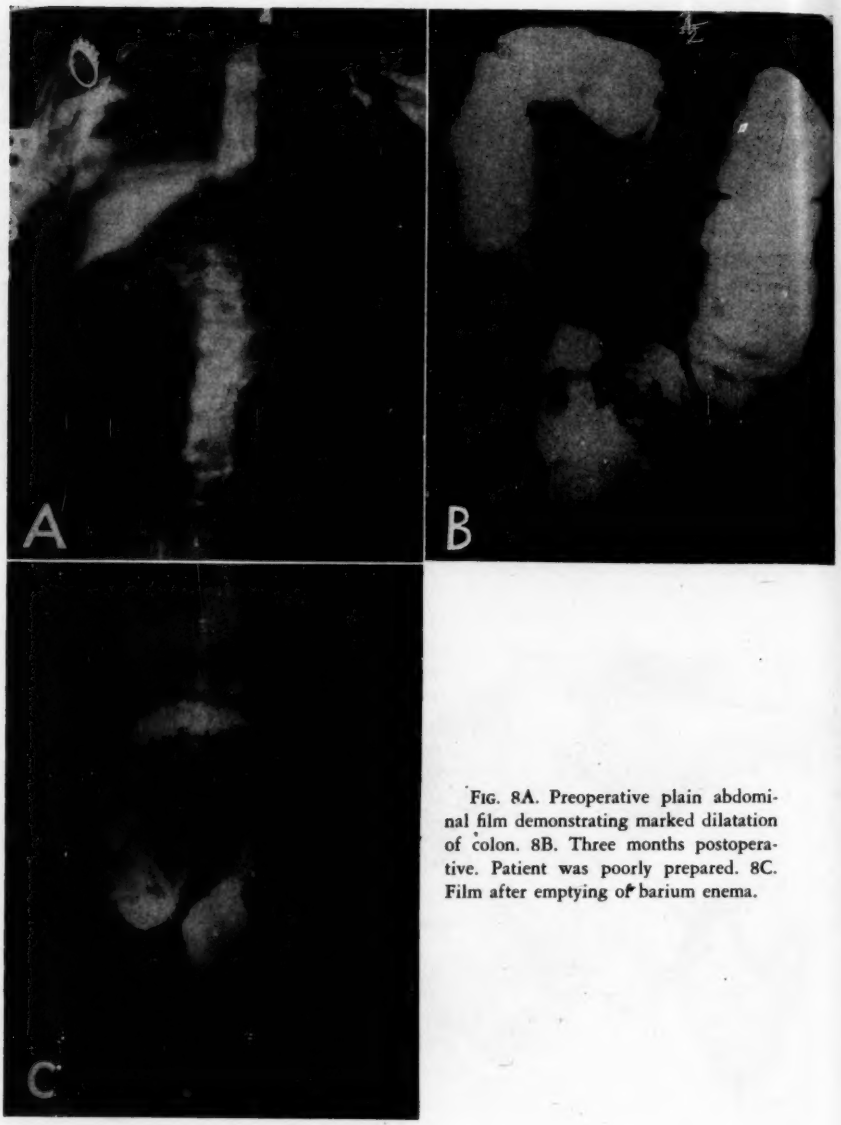

FIG. 8A. Preoperative plain abdominal film demonstrating marked dilatation of colon. 8B. Three months postoperative. Patient was poorly prepared. 8C. Film after emptying of barium enema.

whom the lesion is at the anus (or just above it) and daily rectal dilatation has been sufficient to control the disease.

Summary

Hirschsprung's disease, or congenital megacolon, is due to a functionally abnormal segment of bowel in the sigmoid or rectosigmoid. This can be demonstrated effectively by appropriate roentgenologic studies with barium as a contrast medium. The bowel above this abnormally functioning segment shows changes commonly found above an area of obstruction; the bowel is dilated and hypertrophied.

Removal of the functionally abnormal bowel (rectum or rectosigmoid) has relieved the patients' symptoms. A new operative technique is utilized in performing this resection. The fact is stressed that these children will have to be followed for a period of several years before any claims of a permanent cure can be made.

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Spanish Abstract

Nuevos Conceptos de la Etiología, Diagnosis, y del Tratamiento del Megacolon Congénito (Enfermedad de Hirschsprung)

El megacolon congénito, enfermedad de Hirschsprung, se debe a un segmento funcionalmente anormal del intestino en el sigmoideo o rectosigmoideo. Este puede ser demostrado eficazmente mediante estudios roentgenológicos apropiados con bario como un medio de contraste. El intestino arriba de este segmento que funciona anormalmente revela cambios comunmente encontrados arriba de una area de obstrucción; el intestino está dilatado e hipertrofiado.

Los síntomas del paciente se han mejorado al remover el intestino (recto o rectosigmoideo) que funciona anormal. Se utiliza una nueva técnica operativa al hacer esta resección. El énfasis está en que hay que continuar observando a estos niños por un período de various años antes de poder darlos por curados.

300 Longwood Avenue

WOLFF-PARKINSON-WHITE SYNDROME WITH CONGENITAL HEART DISEASE

By ESTELLE E. KLEIBER, M.D., F.A.C.P.
New Brunswick, N.J.

THE occurrence of a short P-R interval with abnormal and prolonged ventricular complexes in the electrocardiogram was reported in isolated cases as far back as 1915[1] but the attention of cardiologists was focused upon the condition by Wolff, Parkinson and White,[2] and their name has become associated with the syndrome. It has been repeatedly pointed out that this abnormality occurs most often in young healthy adults without cardiovascular disease. Such individuals, however, were found unusually susceptible to attacks of paroxysmal tachycardia and this was the usual reason for consulting a physician. Hunter[3] collected 90 cases, 18 of them associated with various types of acquired heart disease but none of congenital origin were listed. Littman and Tamrower[4] commented on the lack of cases reported in infants or in association with congenital disease.

The syndrome is usually considered due to anomalous ventricular excitation through an accessory bundle of Kent in place of the usual pathway through the bundle of His. This was first offered as an hypothesis[5] and later histologically demonstrated by Wolferth and Wood.[6] It might therefore be expected that a certain number of cases would be found in association with congenital heart disease where defects are frequently multiple. One such case was reported by Bodlander[7] in 1946 in association with coarctation of the aorta, and a second by Stein[8] in 1948 with patent interventricular septum. The following case report presents a third such instance.* The appearance of the child during his first attack of paroxysmal tachycardia is strikingly similar to that published by Bodlander,[7] who mentions spells in which the infant "became pale and acted as if he was in a half-faint; his heart was pounding and he was blue around the mouth."

Aside from susceptibility to attacks of paroxysmal tachycardia, the syndrome presents a favorable prognosis for life and indeed for health. It would appear, however, that this prognosis might be altered in the presence of congenital malformations, with the greater hazard of failure developing during prolonged tachycardia.

CASE REPORT

A 6 yr. old boy (T.G.) was brought in for study with a history of attacks of faintness and weakness accompanied by a fast heart rate. These attacks had occurred frequently in the past few months, especially after exertion, such as physical activity in the school yard. His family history was noncontributory and there was no history of maternal illness during pregnancy.

The mother stated that at the age of 7 mos. the baby had been hospitalized because of a rapid heart. On investigation of his hospital record, it was found that the baby was admitted on July 27, 1942 because of weakness and irritability of 2 wks.' duration. His mother had noted poor appetite and occasional vomiting. The baby at intervals seemed to faint and turn pale, had a grunting type of breathing and had become progressively worse before admission. His hospital record described him

(Received for publication Nov. 13, 1948.)

* Since this article was received for publication, another case has been reported in an infant. See Richmond, J. B., Moore, H. R., and Kallen, I. R., Wolff-Parkinson-White syndrome: Unusual case in infant, PEDIATRICS 1:635, 1948.

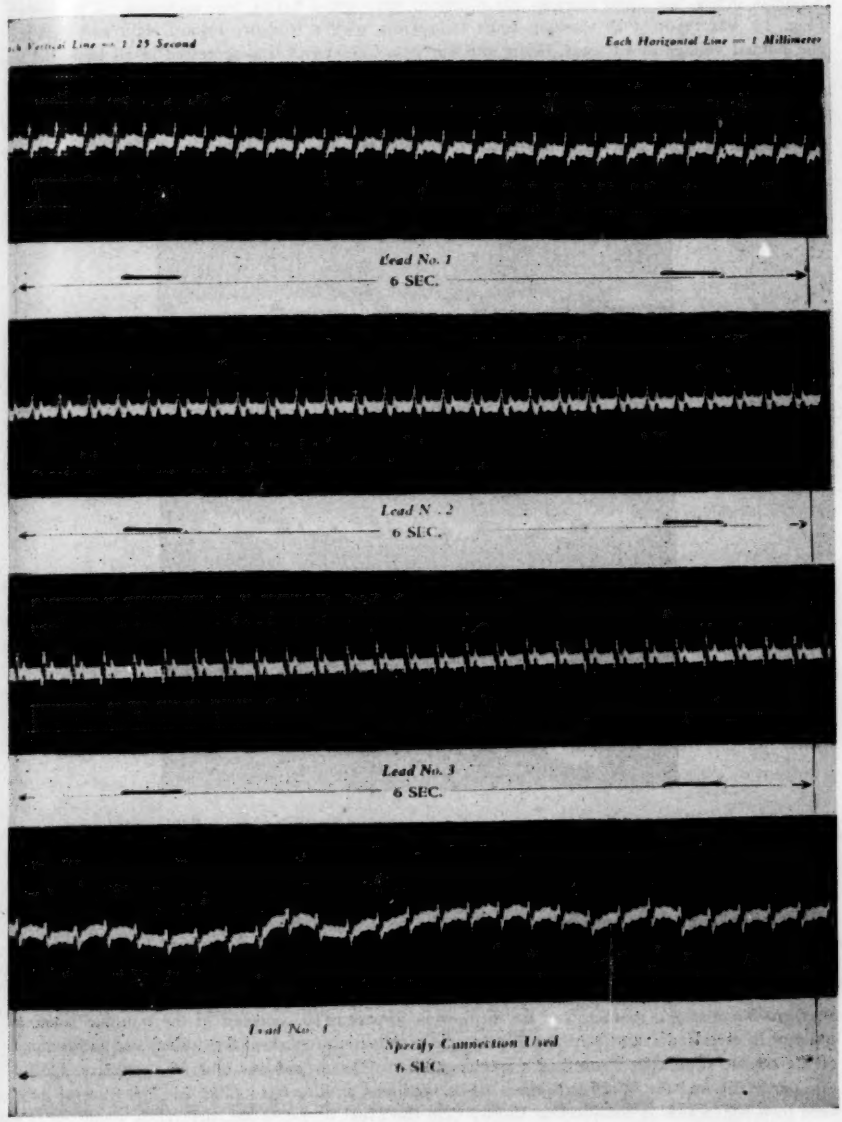

FIG. 1. Electrocardiogram at age of 7 mos. during attack of paroxysmal tachycardia.

as a moderately ill, listless infant, breathing rapidly (36 times/min.) with an expiratory grunt. Lips were cyanotic, apex impulse was tremendously rapid but regular, heart tones faint, and liver palpable 3 fingers below the costal margin. No murmurs were noted during this admission. A cardiogram (Fig. 1) was reported as showing sinus tachycardia with a tendency toward right axis deviation and normal voltage in all leads. Heart rate was 275. ST interval was depressed in all leads and the T waves diphasic in L-1 and L-4F, upright in L-2 and L-3. At this time RBC was 4.4 million/cmm. with 83% hemoglobin; WBC was 11,000/cmm. with polymorphonuclears 78%, lymphocytes 20% and monocytes 1%. Urine was negative. Liquid preparation of digitalis was given him on admission and after 2 days the heart rate was down to 90 and the drug was discontinued. Unfortunately, no cardiogram was taken at the lower rate or the bizarre nature of the tracing might well have been noted.

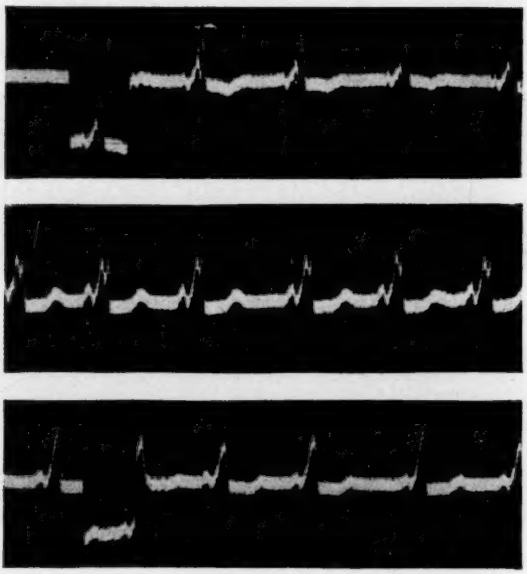

FIG. 2. Electrocardiogram at age of 6 yrs. showing Wolff-Parkinson-White syndrome.

Following this episode, he developed normally and gained weight satisfactorily. A heart murmur was first noted by a physician at the age of 2½ yrs. There were no further attacks of tachycardia until shortly before this admission.

The boy showed no evidence of chest deformity or of clubbing on physical examination. Heart was normal in size and on auscultation sounds were of good quality. A grade 3 systolic murmur was heard over the entire precordium, with maximum intensity in the 3rd left interspace close to the sternum. No diastolic murmur and no thrill were present. The character of the murmur remained constant in erect and supine position. Fluroscopic examination confirmed the normal size and contours of the cardiac silhouette. Urine had a specific gravity of 1.020 and was otherwise negative. Electrocardiogram showed the Wolff-Parkinson-White syndrome as illustrated (Fig. 2). P-R interval measured 0.08 sec. which is considerably shorter than the usual 0.12-0.16 sec. depending upon the rate; the QRS in contrast measured 0.12 sec., the average not exceeding a maximum of 0.10 sec. A diagnosis was made of congenital ventricular septal defect with paroxysmal tachycardia and associated Wolff-Parkinson-White syndrome.

A recent communication from the family stated that no further episodes of tachycardia had occurred in the past year.

Summary

The syndrome of the shortened P-R interval associated with widened QRS as an anomaly of the conduction system of the heart has long been recognized in the adult.

Since few cases of Wolff-Parkinson-White syndrome have been reported in children in association with congenital heart disease, a case report is presented in a boy whose first episode of paroxysmal tachycardia occurred at seven months of age.

The diagnosis of congenital heart disease seems likely in view of the finding of a pronounced, widely heard systolic murmur first noted at the age of 2½ years, and never associated with rheumatism or other signs of infection.

A history of paroxysmal tachycardia in infants and children warrants cardiographic investigation between attacks.

Acknowledgment

Acknowledgment is made to Dr. Ira Degenhardt for access to the earlier records on this child.

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Spanish Abstract

Síndrome Wolff-Parkinson-White con Enfermedad del Corazón Congénita

El síndrome Wolff-Parkinson-White, que consiste de un intervalo de P-R asociado con un QRS ensanchado como una anomalía del sistema de conducción del corazón, ha sido por mucho tiempo reconocido en el adulto. Se ha encontrado más amenudo en adultos jovenes, aparentemente sanos y normales, quienes están, sin embargo, susceptibles a ataques de taquicardia paroxismal. Se han notado pocos casos de este síndrome en niños en conexión con enfermedad congénita del corazón. Este papel presenta un caso de un niño que tuvo su primer episodio de taquicardia paroxismal a la edad de siete meses y después quedó sin síntomas hasta la edad de seis años. La actividad física en la escuela precipitó entonces ataques más frecuentes. La investigación esta vez reveló probable enfermedad congénita del corazón y un electrocardiograma típico. Se citan otros casos en niños pequeños.

131 Livingston Avenue

MECHANISM OF EMERGENCE OF RESISTANCE TO STREPTOMYCIN IN FIVE SPECIES OF GRAM NEGATIVE BACILLI

By HATTIE E. ALEXANDER, M.D., AND GRACE LEIDY, A.B.
New York, N.Y.

A NUMBER of reports[1-7] have presented evidence that failure of streptomycin treatment of infections caused by a number of species of gram negative bacilli is closely related to emergence of resistance of the infecting organism. An understanding of the mechanism responsible for this limitation of the therapeutic value of streptomycin is therefore of great importance. This paper presents evidence on the origin of the resistant members and discusses measures for their control.

It is now well established for some bacterial species that their members which resist certain antibacterial agents arise as the result of mutation and therefore occur spontaneously, independent of the action of the agent. This principle has been shown by a group of geneticists, Luria, Demerec, Fano and Oakberg,[8-12] to apply to E. coli resistant to specific bacteriophage, Micrococcus pyogenes (staphylococcus) resistant to penicillin, M. pyogenes resistant to sulfathiazole, Streptococcus pyogenes resistant to penicillin, and M. pyogenes and E. coli resistant to streptomycin.

Evidence has been presented by Alexander and Leidy[13] for the mutational origin of H. influenzae cells which are resistant in vitro to the action of 1000 mcg. of streptomycin per cc. The presence of such cells in the spinal fluid of patients results in therapeutic failure of this antibiotic.[5] A preliminary report[14] presented data suggesting that streptomycin resistant variants of five different gram negative bacilli of enteric origin are likewise the result of bacterial mutation.

This paper presents the completed experiments of the latter report.[14] Five varieties of gram negative bacilli of the enteric group, E. coli, Salmonellae, Shigellae, S. typhosa and Ps. aeruginosa (pyocyaneus), were examined to determine whether their variant cells which resist the action of streptomycin also arise as the result of bacterial mutation. The following evidence is presented to show that the resistant variants of each of these five species exhibit traits characteristic of bacterial mutants:

1. Demonstration of their independence of the action of streptomycin by showing their continuous irregular occurrence with different prevalence in independent cultures of same population size and strain.

2. Transmission of resistance unchanged in degree through many subcultures in the absence of streptomycin.

3. A low rate of occurrence of the resistant variants, not varying significantly among different strains of the same species.

MATERIALS AND METHODS

Examination for Characteristic 1.—To examine for the 1st characteristic, the following procedures were carried out on each of the 5 organisms. All cultures used were originally isolated

From the Babies Hospital and the Department of Pediatrics, Columbia University, College of Physicians and Surgeons, New York, N.Y.

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from infected patients and preserved by drying and sealing under a vacuum of 10 μ Hg or less (McLeod gauge).[15] The dried culture was seeded in 60 to 70 cc. of Levinthal broth in a 300 cc. Erlenmeyer flask and incubated 16 to 18 hrs. at 37° C.; this culture was inoculated in 0.5 cc. quantities on the surface of 10 or 20 plates of Levinthal agar. After a 5 to 6 hr. incubation period, the growth on each plate was removed by washing with a constant volume of broth, 3.5 to 4 cc., and pipetted to an individual tube. From each 1 of this series of either 10 or 20 tubes, 1 cc. was transferred to an empty sterile petri dish and 1.2 cc. to a small flask to form a pool which after thorough mixing was transferred in 1 cc. quantities to each of another series of 10 petri dishes. This provided 2 series of 10 or 20 plates, each plate containing approximately the same number of organisms: in 1 series, each plate received its inoculum from an independent culture; in the other each was seeded from the same source, the pool. Melted and cooled Levinthal agar medium containing 1000 mcg. of streptomycin per cc. was added to each of the 1 cc. suspensions in the 2 series of petri dishes and thoroughly mixed. In the tests on Shigella strains proteose #3 agar (Difco) was used in place of Levinthal agar. After an incubation period of 4 days, colony counts were recorded. For practical purposes, all colonies appearing under these conditions are resistant to 1000 mcg. of streptomycin* per cc. In order to determine the number of resistant variants in the initial broth inoculum used for production of large populations for examination, this culture was seeded in 2 cc. quantities into 20 to 25 pour plate preparations of Levinthal agar containing 1000 mcg. of streptomycin per cc. The number of resistant colonies contained in 40 to 50 cc. of this broth culture was determined by counting the colonies after an incubation period of 96 hrs.

Examination for Characteristic 2.—The transmissibility of the trait, resistance to 1000 mcg. of streptomycin per cc., was determined for each species; 2 colonies of each showing equally good growth in the presence and absence of streptomycin were subcultured in Levinthal broth 20 times at 24 to 48 hrs. intervals. After 1, 10 and 20 subcultures, the following procedures were carried out: A broth culture incubated for 18 to 24 hrs. was seeded in a 2 mm. loopful into 2.5 cc. of Levinthal broth in a tube; after 6 hrs. growth 0.5 cc. of the 10^{-7} dilution of the broth culture was seeded into 2 pour plate preparations of Levinthal agar, 1 of them containing 1000 mcg. of streptomycin per cc. The number of colonies in each plate was recorded after 48 hrs. incubation.

Examination for Characteristic 3.—Each of the 5 species was examined to determine the rate of occurrence of the cells resistant to 1000 mcg. of streptomycin per cc. The technics used for this purpose were the same as those described above for study of characteristic number 1 save for 2 modifications. To use the formula offered by Luria and Delbrück[8] for estimating the mutation rate, the data must be derived from experiments in which the resistant colonies growing in pour plates containing 1000 mcg. of streptomycin per cc. cannot originate from those already present in the original broth inoculum used for production of large populations. To eliminate those which may be present in the broth suspension of organisms used to seed the series of plates for production of independent cultures, this inoculum must be diluted; the degree of dilutions varies from 1:10 to 1:1000 in different experiments and is indicated for each. The generation time for these organisms is so short that a good growth is obtained from this inoculum after 6 hrs. incubation. The other modification was the use of proteose #3 agar (Difco) in place of Levinthal agar for pour plate seeding of both independent and pool cultures. Some of the tests on E. coli and Salmonellae, carried out in both of these media, showed no significant difference in results.

Application of the Luria and Delbrück formula has already been described in detail for H. influenzae.[13]

From each of the tests performed for estimating mutation rate on each of these 5 species, a number of the colonies forming in agar pour plates containing 1000 mcg. of streptomycin per cc. were selected for study of their degree of resistance to streptomycin. Each colony selected was suspended in 0.05 cc. of broth; a 2 mm. loopful of the suspension was then seeded on a sector of the surface of a Levinthal or proteose #3 (Difco) agar plate containing 1000 mcg. of streptomycin per cc. and also on part of a plate containing the same media without streptomycin. One eighth of a plate provided adequate testing space for each culture.

Experimental Results

In Table I are listed the results of experiments which examined resistant variants of all 5 species for evidence of their presence in cultures prior to exposure to streptomycin and their irregular

* Streptomycin #457 and purified #4647 was supplied by Chas. Pfizer & Co.

occurrence in different independent cultures of the same strain and population size. For each species there is listed the number of colonies growing per plate in the series in which each was seeded from a different independent culture and also the number per plate in the series derived from a single source, the pool. Even though the plates of each series received approximately the same number of organisms, it is apparent that the resistant variants are irregularly distributed among the different independent cultures in contrast to the even distribution among those seeded from the pool.

A number of strains of each of these 5 species when large populations were seeded for the first time, as agar pour plates containing 1000 mcg. of streptomycin per cc., formed colonies of highly resistant variants. In all experiments in which the populations examined contained a sufficient number of resistant variants to prevent the undue influence of chance, the irregularity of distribution of

TABLE I

COMPARISON OF DISTRIBUTION OF RESISTANT COLONIES IN POPULATIONS OF SAME STRAIN AND SIZE DERIVED FROM MULTIPLE INDEPENDENT SOURCES WITH THAT IN SERIES DERIVED FROM SINGLE CULTURE

Species	Source of Cultures	Total Bacteria Examined	Resistant Colonies	
			Total	Number per plate
E. Coli	Pool	Billions 325	534	50-53-56-45-54-51-44-66-55-60
	Independent Cultures	650	1082	15-36-42-595-45-49-8-13-20-19-20-25-10-22-10-11-11-28-15-88
Salmonellae	Pool	630	100	8-8-13-14-8-13-8-7-9-12
	Independent Cultures	1260	184	6-2-2-10-51-9-6-6-0-0-1-12-2-4-18-8-1-9-17-20
S. typhosa	Pool	440	43	3-6-4-3-3-6-5-4-4-5
	Independent Cultures	880	75	0-0-6-6-5-2-3-5-4-3-1-1-1-1-0-3-3-0-1-30
Shigellae	Pool	110	156	19-17-16-15-13-14-18-13-15-16
	Independent Cultures	110	175	13-40-21-16-13-11-32-14-13-2
Ps. aeruginosa	Pool	87	199	14-20-18-23-13-24-23-23-14-27
	Independent Cultures	87	204	2-23-13-60-3-10-55-9-25-4

resistant colonies was obviously greater among cultures seeded from a number of independent sources than among those derived from a single source. This evidence provides proof of the spontaneous occurrence of resistant cells in each of these species and therefore demonstrates their independence of the action of streptomycin.

Two colonies of resistant variants from each of these 5 species were examined for evidence of inheritance of the resistant trait. For this purpose colonies were selected which produced equally good growth in the presence of 1000 mcg. of streptomycin per cc. and in the absence of this antibiotic. The degree of resistance exhibited after 1, 10 and 20 subcultures in broth in the absence of streptomycin was tested by comparing the number of colonies which grew from the same inoculum when seeded into pour plates of Levinthal agar in the presence and absence of 1000 mcg. of streptomycin per cc. Table II presents the results of these examinations. It is apparent that there was not a

significant difference between the number of colonies growing from the same inoculum in the presence and absence of 1000 mcg. of streptomycin per cc. after 1, 10 or 20 subcultures in the absence of streptomycin. The resistant trait is transmitted unchanged in degree and can therefore be presumed to be inherited.

Three types of strains of each species were examined by procedures which provided data from which the rate of occurrence of the resistant variants could be calculated by using the formula of Luria and Delbrück.[8] The data are listed in Table III.

When the average number of resistant colonies per plate and the number of plates used are known, the value "aN_t" can be read from a graph; with a finite value for "aN_t," the rate of occurrence of resistant cells per bacterium per bacterial generation can be determined.

TABLE II

INHERITANCE OF RESISTANCE (1000 mcg. OF STREPTOMYCIN PER CC.) TRAIT BY DESCENDANTS OF VARIANT CELLS FORMING COLONIES DURING FIRST EXPOSURE TO STREPTOMYCIN (1000 mcg. OF STREPTOMYCIN PER CC.)

Species	Colony Number	Colonies Growing from Equal Inocula in Presence and Absence of Streptomycin* After 1, 10 and 20 Subcultures Free of Streptomycin					
		1		10		20	
		0†	1000 mcg.‡	0	1000 mcg.	0	1000 mcg.
E. coli	1	100	118	60	46	64	88
	2	118	122	60	52	90	54
Salmonellae	1	60	88	82	82	80	96
	2	68	70	152	126	40	60
S. typhosa	1	46	22	46	46	58	42
	2	76	108	88	60	84	56
Shigellae	1	52	50	22	25	42	45
	2	36	44	13	14	29	55
Ps. aeruginosa	1	14	10	12	18	62	54
	2	30	24	14	14	94	105

* 1000 mcg. of streptomycin per cc.
† Streptomycin free.
‡ Per cc.

This method provides only an approximate rate; therefore, the small difference among some tests on the same species cannot be considered significant. It is also apparent that the rate of occurrence of these highly resistant variants is not different among the several species of enteric gram negative bacilli tested, nor do they differ significantly from rates already found for H. influenzae.[13]

Table IV lists some growth characteristics of a representative number of resistant colonies of each species, selected from those grown in experiments studying the mutation rate. It is apparent that in each of these species it was possible to demonstrate that a fraction of the resistant colonies cultivated on agar containing 1000 mcg. of streptomycin per cc. differed from the majority, which grew equally well in the presence and absence of streptomycin; they grew poorly or not at all in the absence of

TABLE III

DATA FROM EXPERIMENTS WHICH STUDIED RATE OF OCCURRENCE OF MUTANTS RESISTANT TO 1000 mcg. OF STREPTOMYCIN PER CC.

Species	Type or Strain	Broth Inoculum Used for Seeding Independent Cultures			Resistant Colonies in Independent Cultures			
		Prevalence Resistant Colonies before Dilution	Dilution Seeded	Total Organisms Seeded	Number of Cultures	Average No. Resistant Colonies per Culture	Organisms per Culture Billions	Mutation Rate per Bacterium per Bacterial Generation
E. coli	acid-lactici	1:0.38×10^9	1:1000	6.5×10^6	10	61.8	16.6	7.7×10^{-10}
	communior	1:0.52×10^9	1:1000	9.7×10^6	10	8.0	10.6	2.3×10^{-10}
	acid-lactici	1:0.65×10^9	1:100	3.4×10^7	10	34.0	32.5	2.3×10^{-10}
Salmonellae	newport	1: 5.7×10^9	1:100	5.7×10^7	10	2.4	12.2	8.9×10^{-11}
	typhi-murium	1: 4.0×10^9	1:100	6.0×10^7	10	6.8	12.8	1.7×10^{-10}
	newport	0:10.2×10^9	1:100	5.1×10^7	10	17.1	13.7	3.1×10^{-10}
S. typhosa	Strain 1	0: 4.9×10^9	1:100	4.7×10^7	10	0.7	5.1	1.0×10^{-10}
	Strain 2	0: 3.9×10^9	1:10	3:9×10^8	10	4.4	10.4	1.6×10^{-10}
	Strain 3	1: 7.0×10^9	1:10	6.9×10^8	10	2.4	18.5	5.3×10^{-11}
Shigellae	sonnei	1:0.02×10^9	1:1000	9.0×10^6	20	6.1	5.1	3.3×10^{-10}
	alkalescens	1:2.5 ×10^9	1:100	6.2×10^7	10	17.5	11.0	3.8×10^{-10}
	paradysenteriae	0:7.0 ×10^9	1:100	7.0×10^7	10	7.6	4.5	5.3×10^{-10}
Ps. aeruginosa	Strain 1	1:0.39×10^9	1:100	3.7×10^7	10	3.3	2.2	6.0×10^{-10}
	Strain 2	1:0.39×10^9	1:1000	1.7×10^7	10	2.4	2.3	4.6×10^{-10}
	Strain 3	1:0.14×10^9	1:500	1.2×10^7	10	2.2	2.4	4.2×10^{-10}

TABLE IV

GROWTH CHARACTERISTICS OF COLONIES WHICH FORM IN MEDIA CONTAINING 1000 mcg. OF STREPTOMYCIN PER CC.

Species	Total Resistant Colonies Studied	Number of Colonies Showing Following Traits	
		Comparable Growth In Presence and Absence of Streptomycin*	Grow Well on Streptomycin* Agar Poor or no Growth without Streptomycin
E. Coli	90	64	26
Salmonellae	120	106	14
S. typhosa	104	96	8
Shigellae	109	72	37
Ps. aeruginosa	76	68	8

* 1000 mcg. per cc.

streptomycin. The problem of streptomycin requirement will be discussed in more detail in a report to be published on the behavior of these streptomycin dependent mutants.

Resistant variants dependent upon streptomycin for their growth have been described for type b H. influenzae,[18] N. meningitidis,[16] E. coli, Proteus morgani, M. pyogenes, Ps. aeruginosa and K. pneumoniae,[17] B. subtilis[18] and M. ranae.[19]

Discussion

The results of these investigations on resistant variants of each of five gram negative bacterial species provide evidence that they arise as the result of bacterial mutation.

The presence of resistant mutants offers one explanation for the limitations of the therapeutic efficacy of streptomycin in severe infections caused by these organisms. When the bacterial population is sufficiently large, the chances for the initial presence of highly resistant mutants are good. The sensitive members are killed off leaving a small number of resistant mutants. There is clinical and bacteriologic improvement for a while; but, since these mutants can thrive in the presence of 1000 mcg. of streptomycin per cc. and since they breed true, the strain emerges resistant and the infection recrudesces; the organisms are now insensitive to high concentrations of streptomycin.

However, the great difference in therapeutic efficacy of streptomycin among infections caused by the eight different species of gram negative bacilli already studied[13, 20] is unexplained by the rate of occurrence of their highly resistant mutants. Subsequent studies to be reported later have shown that the rate of occurrence of mutants possessing a lower degree of resistance (25 and 100 mcg. of streptomycin per cc.) exerts an important influence and helps to explain the differences in therapeutic success of streptomycin among these infections.

Among the resistant mutants of each of these five organisms, there are some which behave differently from the majority; they grow well in medium containing 1000 mcg. of streptomycin per cc. but poorly or not at all in the absence of streptomycin, as if this antibiotic furnishes a growth substance needed to meet the changes in nutritional requirements. There is reason to believe that the latter changes result from an additional mutation, presumably involving genes different from those responsible for resistance to streptomycin. These facts raise the question whether the continuation of streptomycin after emergence of resistance of a strain may make the infection worse.

It is obvious that an increase in therapeutic dose cannot control these highly resistant mutants. There is every reason to believe that these resistant cells can be eliminated in each of these species of gram negative bacilli by an effective agent which operates through a different mechanism. For example, H. influenzae cells which resist the action of 1000 mcg. of streptomycin per cc. exhibit the usual degree of sensitivity to sulfadiazine in vitro.[13] Moreover the therapeutic efficacy of streptomycin is greatly enhanced by the addition of sulfonamides.[21] The results of preliminary experiments indicate that the streptomycin resistant mutants of E. coli and Shigellae also show normal sensitivity to sulfonamides. On the other hand, there is no reason to believe that the sulfonamides will prove effective in combating the resistant mutants of Salmonellae, S. typhosa or Ps. aeruginosa. Polymyxin B or aureomycin may provide the action needed; preliminary studies suggest that variants of gram negative bacilli which are resistant to high concentrations of streptomycin will prove to be sensitive to polymyxin B.[22]

Summary

The following evidence has been presented as proof of the mutational origin of streptomycin resistant variants of five different species—E. coli, Salmonellae, Shigellae, S. typhosa and Ps. aeruginosa:

1. Demonstration of their independence of the action of streptomycin by showing their continuous irregular occurrence with different prevalence in independent cultures of same population size and strain.

2. Transmission of resistance unchanged in degree through many subcultures in the absence of streptomycin.

3. A low rate of occurrence of the resistant variants, not varying significantly among different strains of the same species.

A fraction of the resistant mutants of each of these five organisms grows poorly or not at all in the absence of high concentrations of streptomycin.

The therapeutic implications of these facts are discussed.

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SPANISH ABSTRACT

Mecanismo de Emergencia de Resistencia a la Estreptomicina en Cinco Especies de Bacilos Negativos "Gram"

La siguiente evidencia se ha presentado como prueba del origen mutacional de las variaciones, resistentes a la estreptomicina, de cinco diferentes especies: E. Coli, Salmonellae, Shigelae, S. typhosa y P. aeruginosa:

1. Demostración de su independencia de la acción de la estreptomicina revelando su aparición irregular continua con diferente predominio en cultivos independientes del mismo tamaño y esfuerzo de población.

2. Trasmisión de resitencia inalterada en grado al traves de muchos subcultivos en la ausencia de la estreptomicina.

3. Un tipo bajo de aparición de las variaciones resistentes, sin variar significativamente entre esfuerzos diferentes de las mismas especies.

Una fracción de mutantes resistentes de cada uno de estos cinco organismos crece muy mal o no crece para nada en la ausencia de altas concetraciones de estreptomicina.

La presencia de mutantes resistentes ofrece una explicación para las limitaciones de la eficacia terapeutica de la estreptomicina en infecciones severas causadas por estos organismos. Cuando la población bacterial es suficientemente grande, la posibilidad de la presencia initial de mutantes altamente resistentes es buena. Los miembros sensitivos son matados, dejando un número pequeño de mutantes resistentes. Hay un mejoramiento clínico y bacteriológico por un rato; pero como estos mutantes pueden prosperar en la presencia de 1000 mcg. de estreptomician por cc. y como se multiplican el esfuerzo hace surgir resistentes y la infección se recrudece; los organismos están ahora insensitivos a altas concentraciones de estreptomicina.

Es evidente que un aumento en dosis terapéutica no puede controlar estos mutantes altamente resistentes. Hay razón para creer que estas células resistentes pueden ser eliminadas en cada una de estas especies de bacilos negativos "gram" mediante un agente eficaz que opera por medio de un mecanismo diferente. Por ejemplo, células influenzae H. que resisten la acción de 1000 mcg. de estreptomicina por cc. muestran el grado usual de sensitividad a la sulfadiazina in vitro. Además la eficacia terapéutica de la estreptomicina es aumentada grandemente mediante la adición de sulfonamides. Los resultados de los experimentos preliminares indican que los mutantes resistentes a la estreptomicina de E. coli y Shigellae también muestran sensitividad normal a sulfonamides.

622 West 168th Street

STUDIES IN PANCREATIC FIBROSIS

A Simple Diagnostic Gelatin Film Test for Stool Trypsin

By HARRY SHWACHMAN, M.D., PAUL R. PATTERSON, M.D., AND JOSÉ LAGUNA, M.D.
Boston, Mass.

THE number of cases of pancreatic fibrosis recognized by the clinician has increased many fold during the past 10 years. That this disease is not an uncommon one is attested by the fact that over 70 patients with pancreatic fibrosis were seen during the past year in this clinic. Conclusive diagnostic evidence is the demonstration of absent or markedly reduced enzyme activity of aspirated duodenal fluid; provided, of course, that local conditions such as pancreatic duct obstruction, congenital anomalies or rare systemic disorders involving the pancreas, such as syphilis or hemochromatosis, can be ruled out. The assay of duodenal fluid for trypsin by its action on a gelatin substrate is considered adequate for diagnosis, inasmuch as the absence of trypsin is usually accompanied by absence of lipase and amylase.[1, 2] Rare exceptions to this generalization have been encountered.[2]

In order to avoid the disturbing, time-consuming and occasionally unsuccessful duodenal catheterization, efforts have been directed along other lines as aids in diagnosis. This approach is worth while, as illustrated by the case of a severely ill child in whom the diagnosis of pancreatic fibrosis was strongly suspected on clinical grounds, but in whom each of four separate attempts at duodenal catheterization failed. The child subsequently died with the diagnosis still questioned, only to be verified at postmortem examination. A small number of patients have been seen in whom as many as four or five separate attempts at duodenal catheterization were made by experienced personnel before a satisfactory fluid was obtained. Other situations are encountered where an infant may be considered too sick to attempt the procedure of duodenal intubation. It might be well to point out that the difficulties inherent in duodenal catheterization have made physicians loath to attempt it unless the clinical features were classical, of long-standing, or extreme in degree. No doubt this has led to the recognition of the more advanced cases and has, in general, painted a black prognostic picture for this disease. Suggestions to circumvent duodenal catheterization in making the diagnosis of pancreatic fibrosis have been made by West et al.[3] in their amino acid absorption studies, and by others.[4] Metabolic studies, particularly the nitrogen balance as carried out by Shohl et al.,[5] can furnish the diagnosis but only after a long, costly, impractical and difficult investigation.

The more recent studies of Christensen and Shwachman[6] whereby the plasma glycine response is measured following a test feeding of gelatin have afforded a practical method which is used in this clinic. The procedure still is not simple enough for office or outpatient use. Therefore a study of trypsin activity in the stool has been made. A simple

From the Department of Pediatrics, Harvard Medical School, and the Division of Laboratories, The Children's Medical Center, Boston, Mass.

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test has been devised which permits elimination from further diagnostic study a large proportion of children not having pancreatic insufficiency.

It might be of interest to recall that prior to the introduction of duodenal catheterization in infants by Hess,[7] studies concerning pancreatic function dealt with enzyme activity in the stool. Hahn and Lust[8] reviewed the previous contradictory literature on the presence of trypsin in stools. These authors were able to demonstrate tryptic activity using casein as a substrate in all infants studied, regardless of the pH of the stool, whether from an infant with diarrhea or constipation. They encountered one exception, a poorly nourished child who died two days following the test. In the light of what we now know, this child may have had pancreatic fibrosis. It was also recognized that adults had less tryptic activity in the stool than infants. Schlecht[9] showed that the administration of a laxative to an adult would produce a stool possessing tryptic activity. This action was explained by hastening the passage of the pancreatic enzymes through the gut, inactivation, absorption or destruction presumably being intensified by slow passage. In addition Schlecht demonstrated the disappearance of stool trypsin from dogs immediately following the establishment of a pancreatic fistula. Vercellotti[10] studied stool trypsin using a gelatin substrate in 70 adults who were complaining of various gastrointestinal symptoms. He employed laxatives and suppositories to remove constipated stools, and examined the first liquid stool. Only six negative cases were found and all of these had neoplasm of the pancreas, stomach, or of the biliary tree with pancreatic involvement, verified by postmortem examination. Hecht[11] found trypsin present in the stools of infants with acute and chronic nutritional disturbances. Budde[12] stated that the amount of trypsin present in the stools of infants did not vary with the age of the infant nor with the state of nutrition. Lukacs[13] examined 231 children for the presence of trypsin in the stool and concluded that children with infection and nutritional disturbances have decreased trypsin, and, curiously, that there is from 4 to 10 times the normal amount in children with rickets. Murlin,[14] writing in Abt's Pediatrics in 1923, felt that the method of studying pancreatic efficiency by searching for enzymes in the stools was unsatisfactory "for many factors intervene between the entrance of the enzyme upon the scene of action and its exit, any one of which may render the results quite worthless." Although numerous investigators found trypsin present in the stool of normal infants, no one heretofore has attempted to correlate the absence of stool trypsin with the absence of this enzyme in the duodenal fluid of patients with pancreatic achylia.

Method

The measurement of stool trypsin is simple. Two procedures have been used: (1) a test tube method, and (2) a gelatin film method.[15] The former method is more reliable and reproducible due to the fact that the film substrate in the latter method may change its properties when exposed to different temperatures and stored for varying periods of time. However, the film method offers the advantage of simplicity and convenience and can be used as an office test. Photofilm is less reliable than gelatin film.*

The test tube method is performed as follows:

A ⅕ dilution is made by adding sufficient quantity of feces to 4 ml. of distilled water in a test tube with graduation mark at 5 ml. Further dilution can be made as desired. To 1.0 ml. of a ⅕ and a 1/10 suspension in each of 2 tubes, add 1.0 ml. of a 5% solution of $NaHCO_3$ followed by 2 ml. of a 7.5% gelatin† solution, previously warmed to 37° C. The contents are well mixed and the tubes placed in the 37° C. water bath for 1 hr. and then transferred to an ice bath. At the end of 30 min. the tubes are examined. A control tube contains all the above ingredients except feces.

* Gelatin film refers to the roentgenogram film used in routine practice.

† Knox Gelatin—Johnstown, N.Y. (1 envelope contains 7.5 gm.)

Should the contents remain liquid, the activity is recorded as 4+, whereas a rigid gel indicates no activity.

The gelatin film test is performed as follows:

The stool dilutions are made in water as described above. One large drop (approximately 0.1 ml.) of the well mixed specimen is placed on an unexposed, unfixed gelatin film such as is used in routine hospital practice. The film strip may be clipped to a cardboard to prevent curling. The film is incubated at 37° C. for 1 hr. Although 37° C. is recommended, room temperature is satisfactory if the incubation period is prolonged to 1½ to 2 hrs. After incubation the film is washed in a stream of cold water with gentle rubbing. The result is now apparent. A clearing at the site of the drop indicates enzyme activity. A complete clearing is designated as 4+, and a slight clearing, only at the periphery of the drop, as 1+. If the drop is small or if the concentration of the specimen is too great, the material will dry and cake. Proper bacteriologic precautions should be taken when dealing with cases suspected of enteric infections. Both a ⅕ and a 1/10 dilution of stool have been routinely used. When performing the test for the 1st time or when using new gelatin film, adequate controls should be run. The determination of the end point using normal infant stools or a standard trypsin solution is suggested. Discrepancies between the film and tube methods occurred in less than 1% of the tests. The tube method is more sensitive. For example, a specimen showing a 2+ reaction in the 1/10 dilution and a 4+ in the ⅕ dilution on the film will be strongly positive by the test tube procedure as described, using the 1/10 dilution. However, for the practical purposes

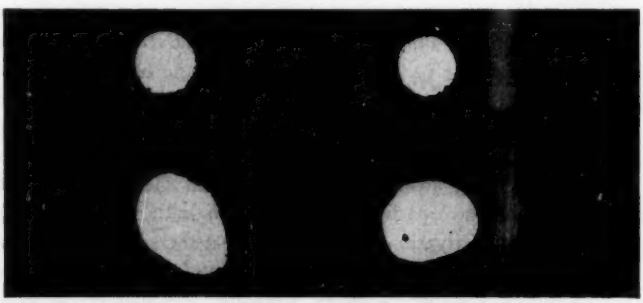

FIG. 1. Appearance of gelatin film showing positive and negative results.

intended, the film method is adequate and is preferable in view of its simplicity and ease of performance. Therefore, only the results by the film technique will be presented here.

Figure 1 illustrates the appearance of a strip of gelatin film acted upon by stool suspensions from 3 individuals. The upper row represents the action of the ⅕ dilution of stool and the bottom row of the 1/10 dilution. Number 1 represents the action of a healthy infant's stool; number 2, that from a patient with pancreatic fibrosis, and number 3, a patient with pancreatic fibrosis receiving oral pancreatin. Note that sample Number 2 in the central position of the figure does not digest the film.

RESULTS

The gelatin film test was performed on stool specimens obtained from normal individuals, from patients with a great variety of illnesses, and from 50 patients with pancreatic fibrosis. Inasmuch as the presence or absence of trypsin is the main concern here, the quantitative data will be omitted and the findings with the ⅕ and 1/10 dilution of stool will be considered. When the ⅕ dilution was 4+ and the 1/10 dilution faintly +, as was noted in a few instances, the stool was considered positive. When a stool is recorded as negative, both the ⅕ and 1/10 dilutions show no perceptible activity.

Table I lists the results obtained in 500 individuals examined, exclusive of patients with pancreatic fibrosis, using the film method. The striking finding is the increasing number of negative tests as one advances into the older age group. All the premature babies studied had tryptic activity in their feces. The smaller babies were fed breast milk and the larger ones received evaporated milk modifications. Many of the premature infants were examined repeatedly with similar findings each time. The infant

TABLE I

STOOL TRYPSIN IN NORMAL AND SICK INDIVIDUALS EXCLUSIVE OF PANCREATIC FIBROSIS, ARRANGED ACCORDING TO AGE

	No. of Cases	Positive Trypsin		Negative Trypsin	
		No. of Cases	Per cent	No. of cases	Per cent
Premature	28	28	100		
Infants	233	223	95.7	10	4.3
2– 5 yrs.	133	117	88.0	16	12.0
5–10 yrs.	74	40	54.0	34	46.0
Over 10 yrs.	32	8	25.0	24	75.0
	500				

group in which the diagnosis of pancreatic fibrosis is most frequently considered makes up the largest number of patients studied. All but 10 of 233 infants examined had a positive stool trypsin test. These 10 cases deserve comment. Two infants had acute severe infections and, when the infection subsided, repeat stool tests showed enzyme activity. Two other infants had large bowel obstruction, and when this condition was relieved, enzyme activity was demonstrated. Another infant had acholic stools due to biliary tract disorder, and when the condition was corrected the test for stool trypsin became positive. In 3 other infants repeat stool examinations became positive and duodenal intubation revealed normal trypsin in the aspirated duodenal fluid. The remaining 2 infants with absent stool trypsin on 1 examination were lost for follow-up study and, insofar as is known, no suspicion of pancreatic fibrosis was raised while they were in the hospital. Included in the infant age group were patients with chronic infections, diarrhea—acute and chronic, pulmonary infections, the celiac syndrome, malnutrition, retarded development and a great variety of miscellaneous disorders. Approximately 25% of the group studied comprised normal, healthy infants. The individuals represented in the age groups 2 to 5 and 5 to 10 are similarly composed of approximately 25% healthy subjects and 75% representing hospitalized individuals. The patients over 10 yrs. of age included many healthy adults, and in this group the great majority had negative tests. Those adults with positive stools were suffering from diarrhea, 2 had sprue, 3 had an acute gastrointestinal upset, and 3 others had diarrhea following a cathartic. The last 3 individuals under normal circumstances had negative stool trypsin tests. It was felt that the cathartic was responsible for the positive result.

During a 7 mo. period, a total of 50 patients with pancreatic fibrosis were examined for the presence or absence of trypsin in their stools. All new patients suspected of having this condition were first subjected to the stool test insofar as this was possible and subsequent work-up included assay of duodenal fluid in all but 1 case for verification of the diagnosis. Gelatin absorption studies[6] were done on many patients in this group. Less than half were patients who had been registered in the nutritional clinic, the diagnosis having been made by finding absent trypsin in the duodenal fluid prior to the beginning of this study. Those receiving oral pancreatin as part of their therapeutic

TABLE II

STOOL TRYPSIN IN PATIENTS WITH PANCREATIC FIBROSIS

	No. of Cases	Positive Trypsin	Negative Trypsin
Infants	29	7	22
2– 5 yrs.	13	0	13
5–10 yrs.	7	0	7
Over 10 yrs.	1	0	1
	50	7	43

TABLE III

RELATION OF NUMBER OF STOOLS EXAMINED TO FINDINGS IN PANCREATIC FIBROSIS

No. of patients examined	No. of stools examined on each	No. of negative stool trypsin	No. of positive stool trypsin
3	1	3	0
17	2	32	2
12	3	31	5
6	4	24	0
3	5	15	0
2	6	11	1
2	7	13	1
2	10	20	0
1	12	12	0
1	18	18	0
1	22	20	2
—	—	—	—
50	220	209	11

TABLE IV

DATA FROM 7 CASES OF PANCREATIC FIBROSIS WITH POSITIVE FINDINGS

Patient No.	No. of stools examined in each patient	No. negative stool trypsin	No. positive stool trypsin
27	22	20	2
47	7	6	1
21	6	5	1
17	3	2	1
36	3	2	1
46	2	0	2
48	3	0	3
—	—	—	—
7	46	35	11

TABLE V

NUTRITIONAL DISORDERS: ASSAY OF DUODENAL FLUID AND STOOL FOR TRYPSIN IN 23 PATIENTS

	Duodenal Fluid		Stools	
	Positive	Negative	Positive	Negative
Infants	16	0	16	0
2– 5 yrs.	3	0	2	1
5–10 yrs.	2	0	1	1
Adults	2	0	2	0

regime were examined while receiving pancreatin, as well as after having this medication discontinued. Two patients died while this study was in progress, and, in both, pathologic changes characteristic of pancreatic fibrosis were found. The results in this entire group are summarized in Table II. Twenty-one patients were over 2 yrs. of age. Although all specimens examined showed absent trypsin, it should be remembered that some normal children in this age group may have similar results. In a small number of patients in this group, the administration of a laxative did not alter the finding of absent trypsin, whereas in a few normal children with absent stool trypsin, a positive result was obtained by this procedure. A disconcerting finding is the presence of trypsin in 7 infants. In 3 of these infants, the diagnosis of pancreatic fibrosis was made in spite of the finding of minimal tryptic activity in the duodenal fluid.

Further examination of this group was considered necessary and a large sampling from patients with pancreatic fibrosis was undertaken. Table III shows the relation of the number of stools examined to the findings in 50 patients. A total of 220 specimens were examined from these 50 patients, with 11 specimens derived from 7 patients showing presence of trypsin and the 209 specimens showing absent trypsin. Data from the 7 cases possessing activity on 1 or more occasions are shown in Table IV.

In patient No. 27, 22 stools were examined. All but 2 were negative. Patients Nos. 47, 36, and 48 were the 3 infants that had minimal tryptic activity in their duodenal fluid. Patient No. 46, now 2 yrs. of age, had meconium ileus at birth, was treated surgically and has absent duodenal trypsin—yet on 2 occasions had a positive stool test. Similarly, Patients Nos. 17 and 21 had no tryptic activity in their duodenal fluid.

Oral pancreatin was given to patients with pancreatic fibrosis almost regularly. As little as ¼ teaspoon of Parke-Davis enteric coated granules, administered t.i.d. with each meal to infants, was sufficient in the majority of instances to render the stool positive for trypsin. In older children, larger doses were often necessary to obtain this result. As might be expected, the administration of an active lipase* preparation did not alter the stool trypsin.

One additional group of patients was investigated (Table V). This included infants with nutritional disorders in whom the stool trypsin was positive. In some the clinical diagnosis of pancreatic fibrosis was suggested and for this reason duodenal intubation was carried out. In these 16 infants, all had normal duodenal trypsin. Of 5 children with normal duodenal trypsin, 2 showed no stool trypsin. Two adults are recorded and both had a sprue syndrome with trypsin present in the duodenal fluid and stool. These cases serve as a control group and demonstrate that infants with positive duodenal trypsin have positive stool activity, an inference drawn from the data in Table I.

Discussion

From theoretical considerations, the proteolytic activity in feces might arise from many sources, including ingested foods and drugs, gastric pepsin, pancreatic and intestinal proteases, intestinal bacteria, or from some combinations of the above factors. The possible action of intestinal parasites, protozoa, and leucocytes, which may be present as a result of disease, will be omitted from consideration. Insofar as food is concerned, few items ordinarily consumed by infants and children possess proteolytic activity in the pH range of normal stools. Of many foods tested on a gelatin substrate, fresh pineapple and honeydew melon were found to have potent proteolytic enzymes. The ingestion of a large amount of pineapple by a child with absent proteolytic activity in the stool did not alter the action of the stool, whereas oral commercial pancreatin resulted in stools possessing proteolytic activity.

Inasmuch as the stools of most adults do not possess gelatin-liquefying activity, it must be assumed that if foods containing this activity were ingested, the numerous conditions to which the enzymes are subjected in the passage of food through the gastrointestinal tract may be sufficient to cause the destruction or the inactivation of its proteolytic activity.

* Furnished by the Upjohn Company, Kalamazoo, Mich.

Gastric pepsin should not be a factor since it is inactive at the usual pH range of stools. The proteolytic ferments of intestinal secretions do not ordinarily attack a protein molecule such as gelatin. The bacterial proteases may be important as numerous microorganisms sometimes normally present in the large bowel are strongly proteolytic. This group includes Pr. vulgaris, Staphylococcus, spp., some strains of C. coli, C. aerogenes, Bacteroides, spp., Clostridia, spp., as well as many other microorganisms. The samples of 24 hour pure cultures of many of the above mentioned microorganisms on the test gelatin film incubated for 60 minutes at 37° C. resulted in no demonstrable activity in the majority of cases. A mixture of stools possessing no tryptic activity with pure cultures of certain of the above mentioned microorganisms likewise gave inconsistent results, with more activity when Pr. vulgaris was used. The bacterial flora of three positive stools from patients with pancreatic fibrosis were studied and all microorganisms isolated were tested for gelatin liquefaction. None of the microorganisms gave a positive spot gelatin film test in one hour. It should be realized that the proteolytic activity of bacteria and of enzymes liberated in fluid culture media is relatively weak when compared with the potent pancreatic trypsin which can be demonstrated by the relatively crude test described. For example, many normal duodenal fluids can be diluted 50 times or more, and one drop of this dilution will contain sufficient proteolytic activity to act on the gelatin film. Such activity is out of range of the bacterial proteases as encountered in the material under consideration. These findings are in agreement with those of Bettoni[16] who demonstrated that measurable proteolytic activity in stools is not due to bacterial action, but that it arises from the pancreas.

One consideration is the possible contamination of the stool specimen with urine. This is of particular importance in infants where such contamination is common. Since most normal urines contain a protease capable of liquefying gelatin, careful attention concerning the collection of the specimen is advisable.

Stools having no tryptic activity when fresh usually have no tryptic activity at the end of 24 hours, but occasionally may become positive after another 24 or 48 hours at room temperature or at 37° C. In a number of instances, negative stools from patients with pancreatic fibrosis remained negative for as long as eight or nine days, although in a few instances faint positive results were detected at the end of three or four days' incubation. For this reason the specimen should be examined within 24 hours of the collection.

Of practical importance is the utilization of the stool test in the office or outpatient department in the management of infants suspected of having pancreatic insufficiency. Should three separate stool specimens be negative, further studies to confirm the diagnosis may be necessary. However, should three separate stool tests in an infant be positive, then one may be justified in excluding the diagnosis of pancreatic fibrosis, with only the rarest exception. In an older child suspected of having the disease, absent trypsin in the stools following a cathartic would yield equally valuable information. The wide employment of this simple test will detect a number of infants not suspected of having pancreatic insufficiency on clinical grounds alone and thereby permit early therapy. In addition, it may reduce the number of infants hospitalized for diagnostic study and in many cases avoid the necessity of duodenal intubation.

Summary

A simple new test is described which estimates roughly the proteolytic activity of stools

by determining their ability to liquefy gelatin. Fecal suspensions are placed upon gelatin film (unexposed and unfixed) and the extent of removal of the gelatin film noted.

Two groups of patients were studied: (a) 500 normal and sick individuals, and (b) 50 patients with pancreatic fibrosis.

In group (a), less than 5% of the infant group lacked this proteolytic power. As one advanced into the older age groups, this percentage increased. The administration of a laxative to some older children with absent tryptic activity resulted in stools possessing tryptic activity.

A total of 220 separate stool specimens were examined from patients in group (b). In 209 specimens, there was no tryptic activity. The remaining 11 specimens from seven patients showed definite tryptic activity. Three patients in this group had minimal tryptic activity in the duodenal fluid.

When oral pancreatin was given to patients with pancreatic fibrosis, the stools became positive for trypsin. When laxatives were given to a few patients with pancreatic fibrosis, the stool trypsin test remained negative.

The duodenal fluid was assayed in a number of infants with acute and chronic nutritional disturbances, and, when tryptic activity was demonstrated in the duodenal fluid, the stools showed the presence of trypsin.

The possibilities of bacterial or food origin of fecal tryptic activity have been considered and largely eliminated.

Three separate stool examinations by this test in infants are proposed as sufficient either to eliminate or to make probable the diagnosis of pancreatic insufficiency. Conclusions and interpretations based on a single examination is hazardous. At least three specimens should be studied and whenever doubt arises duodenal intubation is indicated.

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SPANISH ABSTRACT

Estudios en Fibrosis Pancreática: Un Simple Ensayo Roentgenógrama Diagnóstico Para Tripsina en Deposiciones

Se describe un ensayo simple para la calculación de la tripsina en deposiciones usando tiras de film roentgenógrama sueltas y descubiertas. Se coloca una emulsión de la deposición en el film y después de la incubación se lava en una corriente de agua fría. La presencia de la actividad tríptica se indica por medio del aclaramiento de la gelatina; cuando no hay cambio es que no hay actividad. Este ensayo se hizo con muestras de 500 pacientes normales y enfermos, lo mismo que con 50 pacientes que padecían de fibrosis pancreática. La incidencia de ensayos negativos aumenta con la edad en individuos normales.

Se llevó a cabo un total de 220 ensayos en 50 pacientes con fibrosis pancreática; de todos solamente 11 muestras (de 7 pacientes) revelaron actividad tríptica. Se propone este ensayo como un ensayo de muestra para el estudio diagnóstico, siempre que se hagan tres exámenes separados de la deposición. La efectividad de la pancreatina oral ha sido también seguida por este ensayo.

300 Longwood Avenue

BRONCHIECTASIS IN CHILDHOOD

II. Aetiology and Pathogenesis, Including a Survey of 272 Cases of Doubtful Irreversible Bronchiectasis

By C. ELAINE FIELD, M.D.
London, England

THE final and practical use of almost all medical science is to maintain health and to combat disease in mankind." These words of Sir Thomas Lewis[1] express the purpose of this investigation. In Part I of this study,[2] the clinical aspects of bronchiectasis were described. Part II deals with its predisposing causes and, in Part III, to be published in a later issue, prophylaxis and treatment will be considered.

It has already been demonstrated in Part I that children suffering from bronchiectasis commonly date the onset of their symptoms from an attack of pneumonia or pertussis, particularly in the first year of life. Rubeola, asthma and bronchitis were less commonly

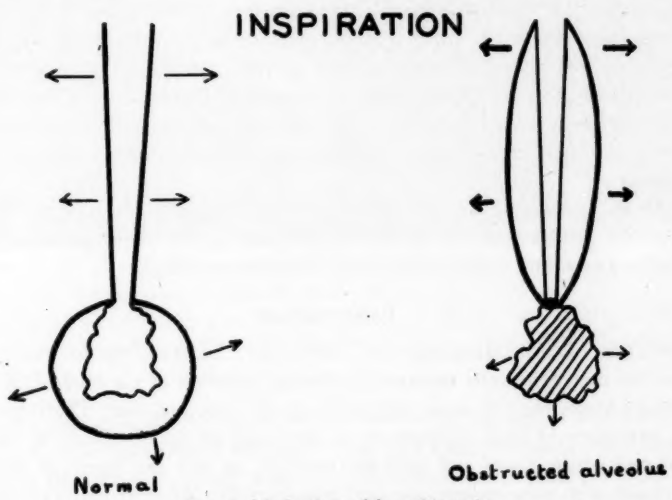

FIG. 1. Mechanism of bronchiectasis

named, and although, in the series reported, foreign body in the bronchus, tuberculous hilar gland and removal of tonsils and adenoids were insignificant as predisposing causes, nevertheless their aetiologic importance is undisputed. The common factor in these conditions is nonaeration of some or all of the alveoli supplied by the bronchus. This nonaeration, resulting from either consolidation or resorption collapse from an obstructed air passage, appears to be the essential factor predisposing to dilatation of the bronchus.

From the Hospital for Sick Children, Great Ormond Street, and University College Hospital, London, England.

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As long as there is a chance for the alveoli to reaerate then the condition is reversible whether infection has occurred or not, but what, if any, is the time limit for this reexpansion is not yet known. Undoubtedly infection predisposes to permanent change but that it is an essential factor is unproved. Infection of the bronchial wall with destruction of supporting elements and later fibrosis renders the wall more susceptible to pressure changes within the chest, these pressure changes being a determining factor in the dilatation. With each inspiration a negative pressure is exerted on all structures in the chest including alveoli and bronchi. If air enters the alveolus, this pressure is prevented from increasing excessively in the bronchi but where entry to the alveolus is obstructed then there must be an increasing negative and therefore dilating force on the bronchial wall (see Fig. 1). Gladnikoff[3] argues on similar lines although he differs slightly on the mechanism of the dilating force.

It may be that within the time limit of a year a certain number of the alveoli reexpand but not all so that an improvement of the dilatation may be observed. Furthermore in children, if hyperplasia of the active elements of pulmonary tissue occurs, then further readjustment of pressures may take place and, providing infection can be reduced to a minimum, then a further improvement may be observed over the years. This improvement has actually been observed. Degrees of dilatation are dependent on the severity of the infection and the dilating forces but there is a type of bronchiectasis often described as varicose bronchiectasis in which there appears to be a weakening of the bronchial wall resulting from infection with minimal alveolar collapse. The dilatation of the bronchus is never gross and the bronchogram suggests dilatation between the cartilaginous rings (Fig. 10, Part I). In this condition, as infection subsides, all symptoms and signs referable to the chest may disappear although the varicose appearance of the bronchial wall persists.

In order to substantiate the statements made in the previous paragraph, the clinical picture of the prebronchiectatic state in a group of children with pulmonary collapse and a further group with doubtful bronchiectasis has been studied.

Pathogenesis

According to McNeil, MacGregor and Alexander[4–6] and Erb,[7] the following sequence of events has been frequently observed. Following infection of the bronchi, as occurs in bronchopneumonia, there is acute ulceration of the bronchial wall. Destruction of the mucous membrane is soon followed by a deepening of the ulceration to involve the muscular and elastic tissue and later the cartilage, so that the bronchial wall is only lined in parts with surrounding collapsed alveolar walls. After varying periods of time, usually about four to six weeks, vascular granulation tissue develops and covers the denuded areas and later the epithelium grows over the nonulcerated areas. This new growth of epithelium may be normal columnar and ciliated, but is more commonly nonciliated cuboidal, squamous or transitional, and is usually arranged in transverse folds. Cartilage, muscle and elastic tissue show no regeneration and fibrous tissue ultimately replaces the granulation tissue. If the infection becomes chronic, fibrosis is progressive, so that ultimately the lobe is practically replaced by fibrous tissue and dilated bronchi (Fig. 2).

It has already been shown in Part I that pneumonia and pertussis were the commonest diseases predisposing to bronchiectasis in the group of 160 cases studied. Bronchopneumonia produces destruction of the bronchial wall as well as collapse and con-

solidation of alveoli. With incomplete resolution, organization of the exudate takes place resulting in permanent de-aeration of alveoli, the essential precursor to bronchiectasis. In some cases, bronchial secretions may obstruct a bronchus producing massive pulmonary collapse. In lobar pneumonia, however, inflammation of the bronchial wall is minimal, resolution is usually complete and bronchiectasis is rarely a complication. The tenacious mucus is probably the important predisposing factor in pertussis. It is difficult to cough up and is therefore liable to produce pulmonary collapse. Those cases that develop from bronchitis and asthma can best be explained on a similar basis, although

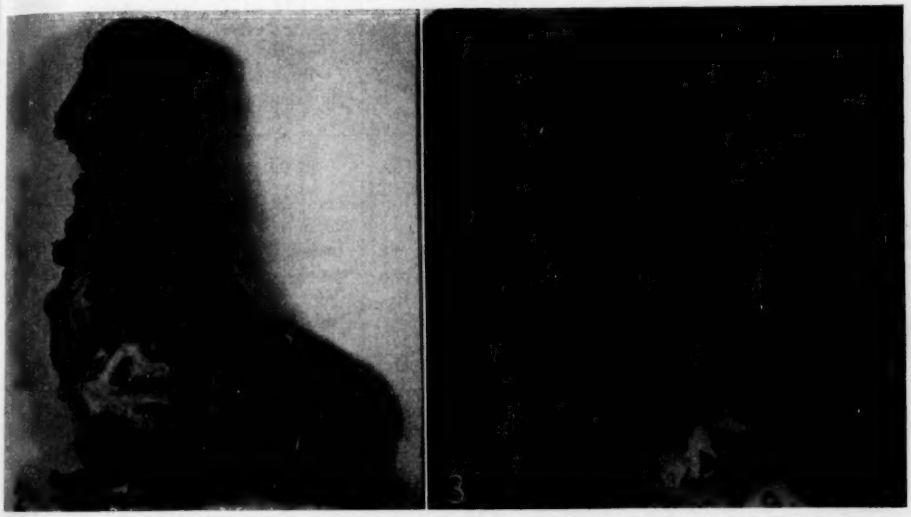


FIG. 2. Section of left lower lobe removed from boy aged 7 yrs. suffering from fusiform bronchiectasis. Note dilated bronchi and extensive peribronchial tissue reaction.

FIG. 3. Right lateral bronchogram from boy aged 8 yrs. taken 3 yrs., 8 mos., after tuberculous hilar gland was visualised occluding right upper lobe bronchus. There is cystic dilatation in anterior part of upper lobe.

bronchial spasm may be a further factor here preventing drainage of secretions. Occlusion of a bronchus by tuberculous granulation tissue or a hilar gland may cause lobar collapse leading to bronchiectasis. This sequence of events is more common than is usually supposed, as has been clearly shown by Jones, Peck and Willis,[8] who demonstrated the presence of bronchiectasis in the bronchograms of 24 out of 34 children with occluded bronchi from tuberculosis. The diagnosis of bronchiectasis is commonly missed because the few symptoms and signs that are present are attributed to the tuberculous condition (Fig. 3). A foreign body producing complete obstruction will also produce pulmonary collapse and if infection is carried in with the foreign body then bronchiectasis is liable to supervene at an early date. However it is possible for a foreign body to remain in situ for years without bronchiectasis developing providing the obstruction is incomplete and there is no infection. Palley[9] comes to similar conclusions on the development of bronchiectasis. Experimental production of bronchiectasis in rabbits has been recorded by Tannenberg and Pinner.[10] Although not comparable with man, many of their findings

support these suggestions despite the fact that their interpretations are open to criticism. For a full account of other theories on the aetiology and pathogenesis, reference should be made to Lisa and Rosenblatt.[11]

If the above-mentioned aetiologic conditions are kept in mind, it is not difficult to explain the selected sites for bronchiectasis to develop. It was shown in Part I that the disease was most common in bronchi whose secretions had to drain against gravity,

TABLE I

NASOPHARYNGEAL INFECTION

Group			I Pulmonary collapse, no bronchiectasis		II Doubtful bronchiectasis		III Irreversible bronchiectasis	
Total number of cases in each group			157		99		160	
			No. of cases	%	No. of cases	%	No. of cases	%
TONSILS	Roentgenogram	Out or small	72	46	46	46½	78	49
		Medium	37	24	18	18	31	19
		Large	31	20	31	31	35	22
		Incomplete data	17	11	4	4	16	10
ANTRA	Proof-Puncture*	Clear	35	30	18	21	21	15
		Thickened mucosa	14	12	11	13	13	9
		Opaque	70	58	56	66	108	76
		Total	119	100	85	100	142	100
		Not done	38	24	14	14	18	11
		Clear	17	36	14	27	20	20
		Mucopus	30	64	38	73	80	80
		Total	47	100	52	100	100	100
		Not done	37	44	15	22	21	17
		Antrostomy	2	1.3	5	5	20	12½
		Caldwell-Luc operation	0	0	9	9	28	17½

* Washouts were only done when roentgenogram showed opaque antra or thickened mucosa and percentage is calculated on this total.

particularly those that showed a bend near the outlet, as in the right middle lobe, or developed a bend as a result of collapse of a neighboring lobe, as frequently occurred with the lingula lobe in collapse of the left lower lobe. These conditions predisposed to retention of secretions and therefore alveolar collapse. Furthermore, bronchopneumonia more commonly occurs in the lower and middle lobes. The upper lobes are rarely affected except following tuberculous occlusion of the bronchus, which most commonly attacks the upper lobe bronchus, and after tonsillectomy, when the positioning of the patient at operation with head downwards encourages aspiration of foreign material into the upper lobes.

It remains to explain why bronchiectasis originates so frequently in early childhood. There are two factors that can be offered as an explanation. The size of a child's bronchus

is relatively smaller and therefore more easily obstructed, and the child is more susceptible to the predisposing diseases of pertussis and respiratory infections.

The Relationship of Sinus Infection and Bronchiectasis

This is a controversial subject. The impression gained from clinical observation is that there exists a close connection between the two conditions without either one being

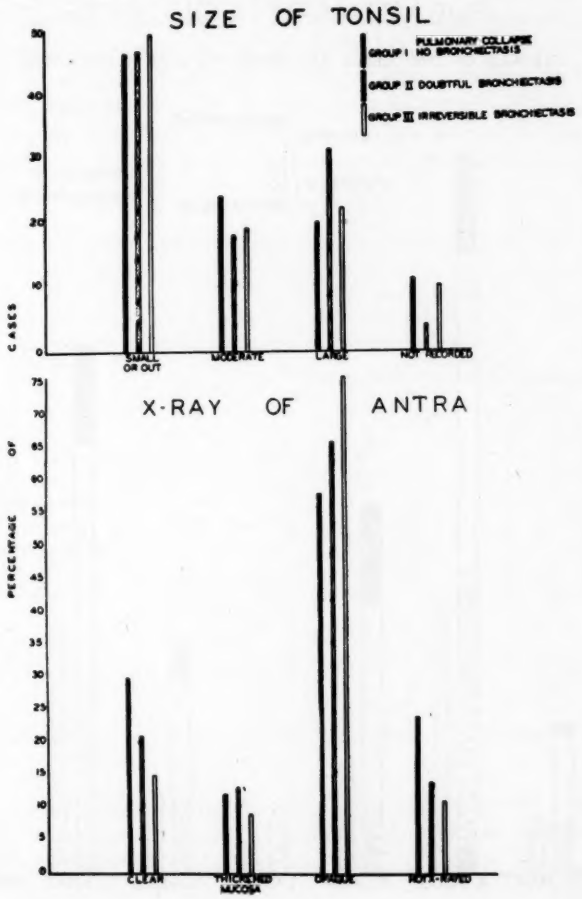


Chart 1

really dependent on the other. The mucous membrane of the nasopharynx and the sinuses is continuous with the bronchial mucous membrane, but apart from this it has been proved by means of lipiodol that secretion in the nasal sinuses will drip into the lungs, particularly when the patient is asleep. (McLaurin[12, 13]). Alternatively, the repeated coughing of a bronchiectatic child must spray the mouth and pharynx with organisms from the lungs, giving an increased susceptibility to nasopharyngeal infection. The figures shown in Table I support these statements.

From Table I and Chart 1 it will be observed that size of tonsil is similar in Group I

and Group III (the prebronchiectatic and bronchiectatic groups) but antral infection according to roentgenogram is present in a higher percentage of cases in Group III, suggesting that bronchiectasis does give rise to a certain amount of antral infection. This was further substantiated on antral washouts. Only cases showing opaque antra or thickened mucosa on roentgenogram received antral puncture. Of these, 64% showed

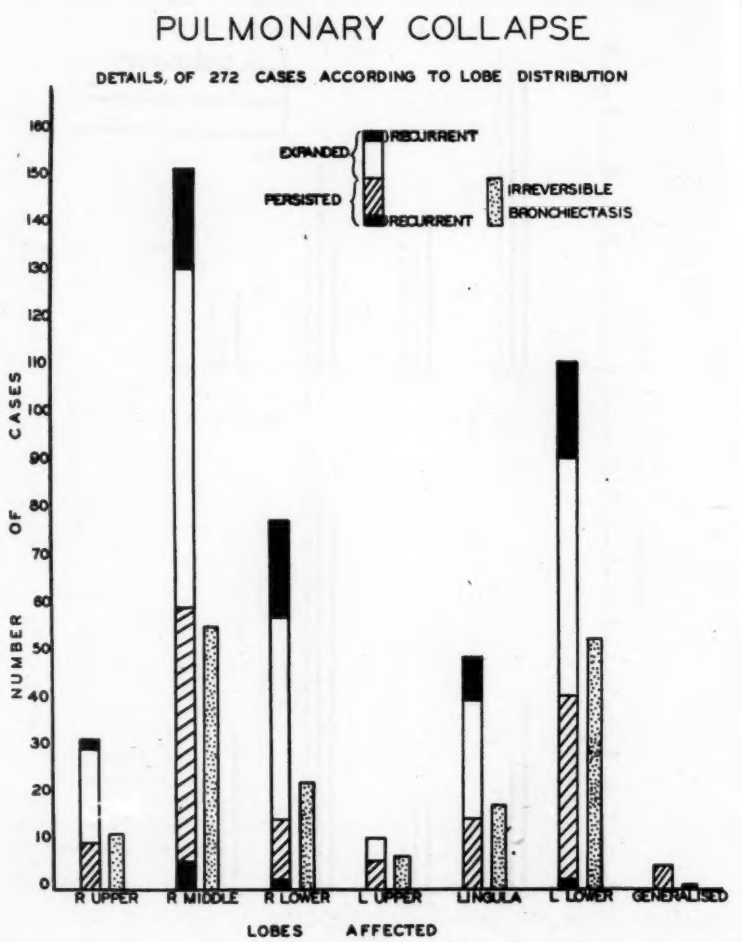


CHART 2

mucopus in Group I, 73% in Group II and 80% in Group III. Most cases showing thickened mucosa gave clear washouts. These figures suggest that an opaque antrum is more likely to show mucopus on puncture in the presence of irreversible bronchiectasis than when associated with pulmonary collapse and no bronchiectasis. It is not justifiable from these figures to assume that antral infection predisposes to bronchiectasis, since nasopharyngeal infection itself may predispose to pulmonary collapse without bronchiectasis; however, it can be shown that sinus infection is not necessary for the develop-

ment of bronchiectasis as approximately a quarter of the known cases in Group III had no evidence of antral infection.

Other authors record sinus infection in from 65% to 80% of patients with bronchiectasis (Davison,[14] Diamond and Van Loon,[15] Walsh and Meyer,[16] Perry and King[17]) but they differ as to the exact relationship of the two infections, although recent work by Walsh and Meyer[16] and Davison[14] suggests that the sinuses and the bronchi are infected at the same time by the same aetiologic factor which commonly seems to be a bronchopulmonary infection in the first decade. McLaurin[12, 13] believes, however, that sinus infection frequently causes bronchiectasis by weakening the bronchial wall. There appears to be no doubt that secretion from the nasopharynx can find its way into the lungs, particularly so in a sleeping patient, but whether this can do any damage in healthy bronchi has yet to be proved. Davison[14] suggests that the double infection may

TABLE FOR CHART 2

272 Cases of Pulmonary Collapse According to Lobe Distribution

	Total Number of Cases	Expanded	Persisted	Recurrent Collapse that finally		Show Irreversible Bronchiectasis	
				Expanded	Persisted	Number	% of Total
RUL	32	22	10	2	0	12	37.5
RML	152	92	60	21	6	56	36.8
RLL	78+1 postoperative	63	15+1	20	2	23+1	29.5
LUL	11+8 postoperative	5+1	6+7	0	0	7+7	63.6
LING	49	34	15	9	0	18	37.8
LLL	111	70	41	20	2	53	47.8
Generalized	5 Autopsy record	0	5	0	0	1	20.0
Total	438	286	152	72	10	170	38.7

It must be appreciated when reading these figures that more than one lobe may be affected in the same child.

be associated with an allergic response to a primary bronchopulmonary infection setting up oedema of the mucous membrane. It is clearly important that the rhinologist must continually remember the possibility of bronchiectasis and the chest physician or surgeon must always examine for sinusitis.

A Clinical Study of 272 Cases of Pulmonary Collapse

The diagnosis of pulmonary collapse was made in this group either by roentgenogram or at autopsy. For the roentgen diagnosis to be made three criteria were followed: 1. The opacity, being the whole or part of a lobe, occupied a smaller area than the normal lobe or a part of a lobe was expected to occupy. 2. One of the margins was concave. 3. If a bronchogram was done, the bronchi showed crowding. This of necessity excluded many cases which might be designated partial collapse where only some of the alveoli were affected producing linear markings rather than a homogenic opacity. Since this study was commenced, however, a better radiologic definition of pulmonary collapse

has been published by Robbins and Hale,[18-23] who utilise the position of the hilum and visible hair-like septa as guides.

This group of cases was collected from children attending the outpatient departments or admitted to the wards of the Hospital for Sick Children, Great Ormond Street, and University College Hospital, London, or their base hospitals over a period of eight years. All cases have been followed for three years or longer for assessment of progress and no case has been described as reexpanded without roentgenogram confirmation. As

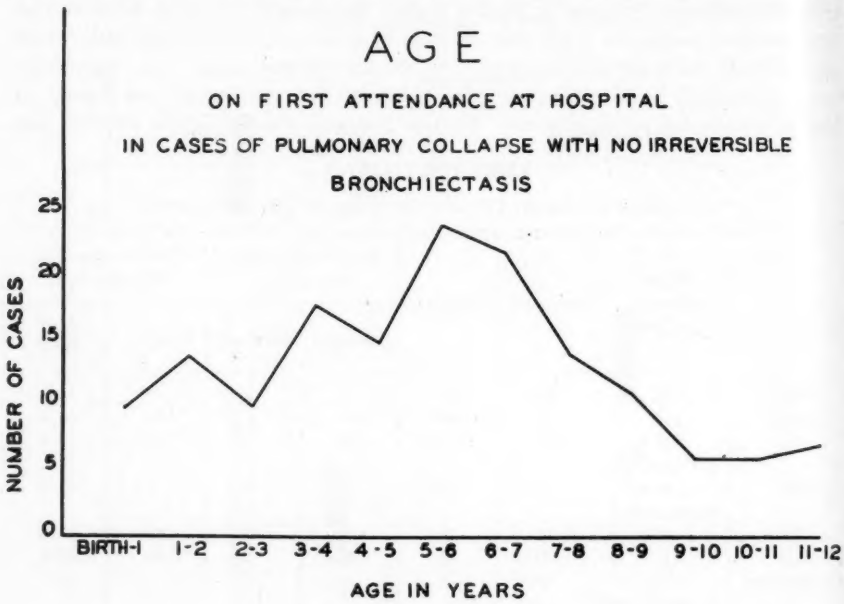


CHART 3

TABLE FOR CHART 3

AGE ON ADMISSION. PULMONARY COLLAPSE. NO BRONCHIECTASIS

Age	0–	1–	2–	3–	4–	5–	6–	7–	8–	9–	10–	11–12	Total
No. of cases	10	14	10	18	15	24	22	14	11	6	6	7	157
Percentage	6.4	8.9	6.4	11.5	9.6	15.3	14.0	8.9	7.0	3.8	3.8	4.5	100

the cases were collected mostly from the wards, the group includes a high proportion of persistent collapse.

It will be noted from Chart 2 that the right middle lobe was the one most commonly affected but also that the left lower lobe was frequently involved. The upper lobes were less frequently involved except postoperatively in the left upper lobe, but when the figures were tabulated according to age the upper lobes showed a similar frequency of involvement to the middle and lower lobes in the first year of life. From these figures the prospect of reexpansion was good in the right lower lobe but poor in the left upper lobe, although the figures for the latter are too small to be of value. The other interesting fact revealed by these figures is the prognosis in cases of recurrent collapse. It was not

TABLE II

CHARACTER OF COUGH

Cough	No. of cases	Percentage
Constant	100	63.7
Intermittent	50	31.8
None	5	3.2
Not specified	2	1.3
Total	157	100

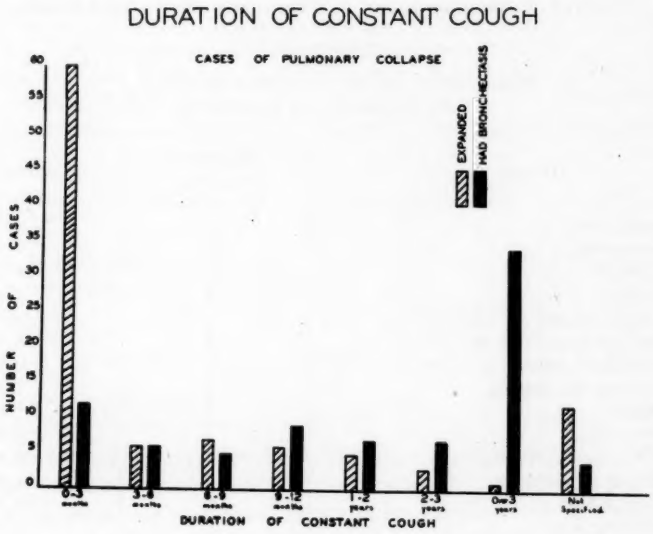


CHART 4

TABLE FOR CHART 4

DURATION OF CONSTANT COUGH. PULMONARY COLLAPSE

Duration of Cough	0–	3/12–	6/12–	9/12–	1–	2–	Over 3	Not Specified	Total
Cases that Expanded	60	6	7	6	5	3	1	12	100
Cases that had Bronchiectasis	12	6	5	9	7	7	34	4	84
Percentage that Expanded	32.6	3.3	3.8	3.3	2.7	1.6	0.5	6.5	100
Percentage that had Bronchiectasis	6.5	3.3	2.7	4.9	3.8	3.8	18.5	2.1	

uncommon for lobes to collapse several times in the same child yet ultimately to expand without bronchiectasis developing. In fact, if a lobe had once expanded after a collapse it appeared to stand a better chance of repeating the performance on successive occasions. Just over a third of the total cases already had or developed bronchiectasis but this group was selective and not representative of pulmonary collapse in general.

Of the 157 children with pulmonary collapse that did not develop bronchiectasis, 82 cases occurred in males and 75 in females. The age distribution is shown in Chart 3. When compared with the age distribution for the bronchiectatic group described in Part I (Chart 1) the findings are similar.

As two-thirds of the children had a constant cough (Table II), this fact was utilised in an attempt to assess duration of the collapse with interesting results.

Chart 4 demonstrates the short duration of cough in those cases of collapse that re-expanded in contrast to the long history in those that showed bronchiectasis.

TABLE III

PREDISPOSING DISEASES (according to the history)
Pulmonary Collapse. No Bronchiectasis

Disease	Number of cases	Percentage
From birth	12	7.6
Pneumonia	15	9.6
Pertussis	23	14.7
Rubeola	8	5.1
Pneumonia and pertussis	9	5.7
Pneumonia and rubeola	5	3.2
Pneumonia, rubeola and pertussis	1	0.7
Pertussis and rubeola	2	1.3
Asthma	6	3.8
Bronchitis	5	3.2
After removal of tonsils	10	6.4
Coryza or sore throat	7	4.5
Foreign body	1	0.7
Miscellaneous	6	3.8
Insidious	21	13.4
Not specified	26	15.6
Total	157	100

In Table III the importance of pneumonia and pertussis as a predisposing cause in pulmonary collapse is demonstrated, 55 cases, 35%, dating the onset of cough from one of these diseases. The other figures of note are 12 cases apparently dating the onset of symptoms from birth, 10 cases from tonsillectomy and the high number (21) with an insidious onset.

Clinical features are shown in Table IV. Cough of varying degree with a slight rise of body temperature and a few localised signs in the chest are all that may signify a pulmonary collapse. However, when associated with infection, pneumonic symptoms and signs may be present.

It is interesting to note that five cases developed clubbing, three of which cleared when the lung reexpanded; the two cases where it has persisted are bad cases of asthma

and may be developing bronchiectasis, no recent bronchograms having been taken. The high figure for pyrexia on admission may be deceptive as the fever had usually subsided in 24 hours and children not uncommonly run a slight fever when first admitted to a hospital. However, at the onset of a pulmonary collapse there is frequently some rise of body temperature which usually soon subsides unless there is an associated pneumonic process.

Chest deformity was not common in simple pulmonary collapse without bronchiectasis, a deepening of Harrison's sulcus being noted in eight out of the 90 children not suffering from asthma. However, deformities were present in association with large tonsils or adenoids in four children and with a tuberculous hilar gland in three children. When the collapse was associated with asthma, 32 out of 67 children showed a pigeon

TABLE IV

CLINICAL FEATURES

Pulmonary Collapse. No Bronchiectasis

Clinical features	Number of cases	Percentage
Sputum	49	31.2
Haemoptysis	2	1.3
Wheezing	57	36.3
Dyspnoea	17	10.8
Pain in chest	9	5.7
Loss of weight	12	7.6
Recurrent colds	21	13.4
Clubbing	5 (3 cleared)	3.2
Cyanosis	11	7.0
Pyrexia when first seen	63	40.1
Number of Cases Examined	157	

or barrel chest or a depression deformity. The impression received is that obstructive phenomena to alveolar expansion are liable to produce chest deformities which can be corrected if the obstruction is removed soon enough; otherwise the deformity is liable to persist.

ASSOCIATED DISEASE IN 157 CHILDREN WITH PULMONARY COLLAPSE AND NO BRONCHIECTASIS

Part I gives the criteria for asthma. There were 67 children (42.7%) who had symptoms suggesting asthma, some for a short period only. Comparing this incidence with that given for asthma in association with bronchiectasis, 33.1% (see Part I), it suggests that pulmonary collapse is commonly associated with asthma but that it frequently reexpands without developing bronchiectasis.

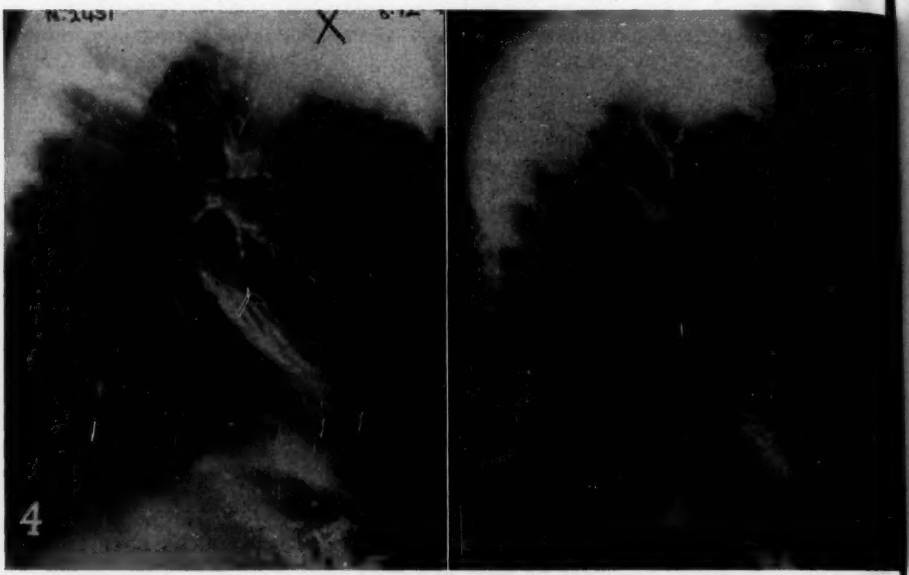
The Mantoux reaction (intradermal 0.1 cc. of 1 in 1,000 Old Tuberculin) was tested in 141 children, giving a negative reaction in 116 and positive in 25 cases. When studying the results according to age groups and comparing with controls (Bradshaw[24]), there was no increased incidence of positive reactors. In 11 out of 12 cases of active tuberculosis a large hilar gland or tuberculous granulation tissue caused partial or complete obstruction of a bronchus.

There was an increased incidence of pneumonia, 48.7% having had pneumonia at

some time compared with only 11% of controls (see Part I), but this is not as high as children with bronchiectasis who gave a 70% incidence.

Nine children had a congenital anomaly. Five of these were in the first year of life and four cases were abnormalities in the heart. These figures are too few for comment.

In 60 cases, one or more bronchograms were performed at varying times after the original collapse was diagnosed. Some degree of dilatation of part of the bronchial tree was noted in 23 of these. (A bronchus was considered to be dilated when its calibre was greater than the calibre of the bronchi going to adjacent parts of normal lung.) In 17 cases there was some crowding of bronchi and 24 cases showed square ends as if a



FIGS. 4 and 5 are bronchographic findings in girl aged 5½ yrs. with temporary collapse of right middle lobe.

FIG. 4. Right lateral bronchogram shows crowding clubbed ends but not much dilatation of right middle lobe bronchi.

FIG. 5. Eleven mos. later showing reexpansion of lobe and normal appearance of bronchi. This unusual case still showed middle lobe opacity in ordinary roentgenogram characteristic of collapse.

dead twig had been snapped off at the tip. There was excessive secretion in 14. Bronchograms were repeated on 24 children usually within one or two years. In 11 of these the dilated bronchi had reverted to normal calibre (Figs. 14 and 15, Part I), and in three patients the collapse and crowding (with dilatation) had cleared (Figs. 4 and 5). In five cases the condition showed improvement and in two cases it appeared to be spreading or becoming more definitely dilated. One child showed improvement on the right side and a deterioration on the left side and two patients had normal bronchograms throughout. Little significance can be attached to these figures because of the varying period after the onset of collapse when the bronchogram was performed. However, they show how variable the picture may be and also demonstrate the importance of recognising reversible bronchiectasis in association with collapse.

Treatment of Pulmonary Collapse

Providing the collapse is of shorter duration than a year, all efforts to assist the lung to expand should be made. After this period, irreversible bronchiectasis has probably occurred and even if the collapsed lobe does appear to expand, as occurred in 19 of these cases, irreversible changes persist in the bronchi. Nevertheless, if in doubt, it is wise to give energetic treatment for the collapse. The method here includes postural drainage all night and for one hour in the middle of the day, the position depending on the site of the collapse (Foster-Carter[25]). Chest clappings while the child is being postured are given night and morning and in the middle of the day; during these, the child is encouraged to cough up secretions. To loosen secretions steam inhalations over a jug of hot water are given three to five time a day, preferably before postural drainage, as well as 8 cc. of Brompton hot water mixture in half a cup of hot water three times a day.

Brompton Hot Water Mixture

Sodium bicarbonate	20 grains
Sodium chloride	3 grains
Emulsion chloroform	5 minims
Emulsion aniside	3 minims
Distilled water	to ½ ounce

For infants a steam tent may have to be erected. Breathing exercises are commenced soon after secretions have loosened and postural drainage instituted. During the day the child is encouraged to run about and play games in the fresh air. If after two to three weeks of this treatment there is no evidence of reexpansion of the lung by roentgenogram, then bronchoscopy is recommended. Formerly, it was done as a routine on all cases but as more success is now attributed to steam inhalations, bronchoscopy is usually deferred unless foreign body is suspected. Of the 272 children with pulmonary collapse 153 were bronchoscoped, 78 reexpanded and 75 developed bronchiectasis. In an attempt to assess the value of bronchoscopy, only those cases with the history of a constant cough of six months' duration or less were analysed. From the figures shown in Table V it appears that bronchoscopy has no influence on pulmonary reexpansion.

TABLE V

Result of Bronchoscopy in Children with Pulmonary Collapse Giving History of Constant Cough of 6 Months' Duration or Less

	Expanded		Bronchiectatic		Total
	Number	Percentage	Number	Percentage	
Bronchoscoped	38	76%	12	24%	50
Not Bronchoscoped	24	80%	6	20%	30

Drug therapy has not been used for pulmonary collapse except to combat acute infections.

Clinical Results

In the 157 children with pulmonary collapse who had no bronchiectasis, 111 were classified as cured with no symptoms or signs after three years' observation, 16 children were improved and 13 children showed no change in their general condition. Of these

last two groups, 23 children suffered from asthma. Six patients, mostly infants, died from associated conditions, and the remainder have been difficult to assess accurately up to date. The conclusion from this data is that the majority of cases are cured except those who suffer from asthma.

Investigations on 99 Cases with Doubtful Bronchiectasis

During this investigation into chronic chest disease in childhood, there was a group of cases that was difficult to classify accurately as either pulmonary collapse or definite bronchiectasis but, because of persistent cough or physical signs in the chest or persistent shadows in the roentgenogram, bronchiectasis was suspected. In many cases bronchograms were done and revealed indefinite bronchial dilatation. Only when the bronchogram was repeated in one or two years' time was the picture clarified. This state of affairs is not

TABLE VI

Analysis of 99 Cases of Doubtful Bronchiectasis

		Number of cases	Percentage
Sex	Male	53	53.4
	Female	46	46.5
Cough	Constant	63	63.6
	Intermittent	33	33.3
	None	3	3.0
Associated Disease	Asthma	47	47.5
	Tuberculosis	7	7.1
	Doubtful Tuberculosis	7	7.1

uncommonly met with in young children and can be considered as the prebronchiectatic state. For this reason a brief analysis of the findings might help to complete the picture of the development of bronchiectasis (see Table VI).

The high number of children suffering from asthmatic symptoms is not surprising in this group as it is sometimes difficult to differentiate asthma from true irreversible bronchiectasis clinically, or even by bronchograms, because the bronchi in chronic asthma often appear a little irregular and pipe-stem in character.

The suspected lobe distribution of the disease did not differ greatly from that recorded for pulmonary collapse and bronchiectasis except that the character was more generalised or diffuse.

The naso-pharyngeal infection in this group has already been discussed (Table I and Chart 1).

Progress

After three years or more under observation the children's progress was assessed symptomatically and the diagnosis reclassified according to the recent investigations (see Tables VII and VIII).

All the children were cured except those classified as irreversible bronchiectasis and some of those still classified as doubtful bronchiectasis. All this last group have been examined with bronchograms and 25 of the 31 showed slight bronchial dilatation frequently of the varicose type. Twenty cases had bronchi with square ends and 13 had excessive secretion of the bronchi. In 15 cases there was slight crowding of the bronchi but insufficient to classify them as pulmonary collapse. Eleven children had repeat bronchograms after one or two years. In four of these the dilated bronchi had reverted to normal calibre, in four the condition had improved; in two it was worse, and in one child part had improved and part had deteriorated. A large number of these 31 children suffered from asthma.

This data on 99 cases of doubtful bronchiectasis demonstrates the importance of a

TABLE VII

CLINICAL RESULTS OF 99 CASES OF DOUBTFUL BRONCHIECTASIS

	No. of cases	Percentage
Cured	37	37.3
Improved	36	36.3
No change	18	18.1
Worse	1	1.0
Died	1	1.0
Inadequate follow-up	6	6.0

TABLE VIII

RECLASSIFICATION OF 99 CASES OF DOUBTFUL BRONCHIECTASIS AFTER THREE OR MORE YEARS' OBSERVATION

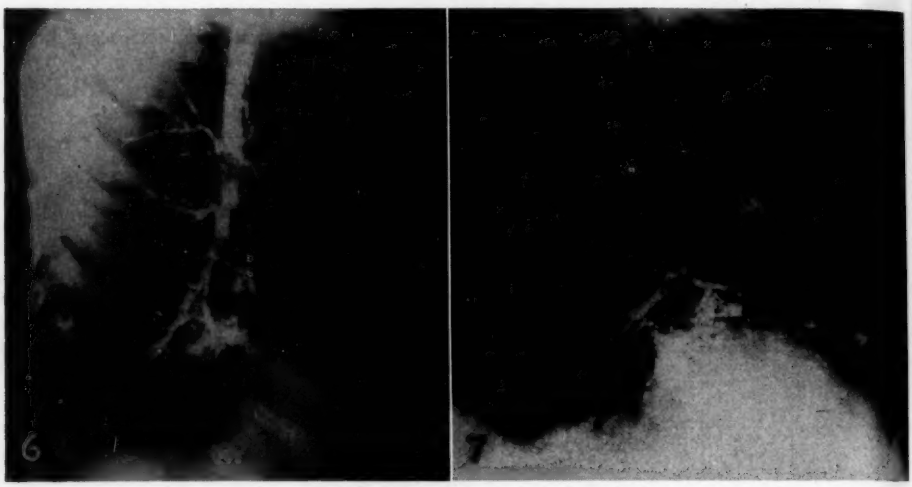
	No. of cases	Percentage
Irreversible bronchiectasis	40	40.4
Pulmonary collapse	11	11.1
Temporary roentgenographic shadow	11	11.1
Miscellaneous	3	3.0
Failed to attend	3	3.0
Still doubtful bronchiectasis	31	31.3

period of observation on all children in which the diagnosis of bronchiectasis is in doubt. The bronchogram should be repeated in one or two years' time when in a large number of cases the picture will be more definite and either the condition will have cleared, or definite bronchiectasis will have developed (Figs. 6 and 7). What actually determines progression or regression of the disease is difficult to assess; probably a combination of factors including drainage of secretions, virulence of the infection and resistance of the host are responsible. Control of infection, assistance of drainage of pulmonary secretions and general convalescence appear to be the chief weapons of defence.

CONCLUSIONS

This clinical study of the prebronchiectatic state in children has revealed the importance of recognising and adequately treating without delay certain predisposing conditions before irreversible changes have occurred leading to bronchiectasis. Of the predisposing conditions, most important are pneumonia, pertussis and pulmonary collapse.

The duration of a constant cough is a useful guide. If it continues for six weeks or longer after the initial acute illness, full investigations should be carried out and all possible means of treatment instituted. A chronic cough should not be allowed to continue with just cough mixture treatment. Persistent de-aeration of alveoli, as may result from collapse or consolidation, seems to be the primary lesion in most cases of bronchiectasis, infection being a superadded cause. In treatment, therefore, it is necessary to combat infection and loosen secretions so that with adequate postural drainage every chance is given to re-aerate the alveoli. Treatment will be discussed more fully in Part III



FIGS. 6 and 7 are from boy aged 5 yrs. whose clinic condition rapidly deteriorated over period of 10 mos.

FIG. 6. Right lateral bronchogram showing collapse with some tubular dilatation of right middle lobe. Incomplete filling of pectoral branch.

FIG. 7. Two yrs., 2 mos. later showing almost cystic dilatation of pectoral and right middle lobe bronchi.

(to be published later). Nasopharyngeal infection frequently occurs in association with pulmonary infection and should be treated at the same time. Either condition may predispose to the other, yet both conditions can exist separately. Although children are more susceptible to the prebronchiectatic state as a result of the small size of their bronchi which easily become blocked with secretion and owing to their susceptibility to infection, yet they have a much greater recuperative power than adults if adequate treatment is instituted.

SUMMARY

Non-aeration of alveoli is a feature common to the childhood illnesses predisposing to bronchiectasis and is regarded as the important factor in the aetiology of the disease, infection playing a subsidiary part.

Pulmonary collapse is therefore regarded as a prebronchiectatic state and in order to assess its importance two groups of cases have been studied: (1) 272 cases of pulmonary

collapse; (2) 99 cases in which the diagnosis of bronchiectasis was doubtful at first examination.

Pulmonary collapse was seen most frequently in the right middle lobe and left lower lobe. It was usually persistent in the left upper lobe but frequently the right lower lobe reexpanded.

The duration of cough, according to the history, was commonly of three months' duration or less in cases of pulmonary collapse that reexpanded, in contrast to the long history of two years or more in the majority of cases that developed bronchiectasis.

Of the 272 cases of pulmonary collapse, only 157 reexpanded without permanent bronchiectatic changes. It was not uncommon, however, to find temporary bronchial dilatation in this group, the bronchi returning to normal calibre when the collapse reexpanded—a condition described as reversible bronchiectasis.

The treatment recommended for pulmonary collapse includes steam inhalations, postural drainage, and breathing exercises. Unless foreign body is suspected, immediate bronchoscopy is no longer considered necessary. No significant difference in the incidence of reexpansion of the lung was found between the cases treated with bronchoscopy and those treated without.

Ninety-nine cases were classified as doubtful bronchiectasis when first seen. Of these, 47.5% suffered from asthma, a disease frequently difficult to differentiate from bronchiectasis. Forty of the 99 cases have now developed true irreversible bronchiectasis after a period of three or more years. It was necessary to observe cases showing doubtful bronchial dilatation over a period of years, the bronchograms being repeated at intervals in order to determine the permanently diseased parts.

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SPANISH ABSTRACT

Bronquiectasia en la Niñez: II. Etiología y Patogénisis, Incluyenda un Estudio de 272 Casos de Bronquiectasia Irreversible Dudosa

La no-aeración de alvéolos es una característica común en las enfermedades de la niñez predisponente a bronquiectasia y se le considera como el factor importante en la etiología de la enfermedad, la infección desempeña un papel subsidiario. El colapso pulmonar es, por consiguiente, mirado como un estado prebronquiectático y con el fin de apreciar su importancia se han estudiado dos grupos de casos: 1. 272 casos de colapso pulmonar; 2. 99 casos en los cuales la diagnosis de bronquiectasia estaba dudosa al primer examen.

El colapso pulmonar se ha visto más frecuentemente en el lóbulo del medio derecho y el lóbulo inferior izquierdo. Generalmente estaba persistente en el lóbulo superior izquierdo; pero frecuentemente el lóbulo inferior derecho se volvía a ensanchar.

La duración de la tos, según los datos, era de tres meses o menos en casos de colapso pulmonar que se re-ensanchaba, en contraste con la larga historia de dos años o más en la mayor parte de los casos que desarrollaron bronquiectasia.

De los 272 casos de colapso pulmonar, solamente 157 se re-ensancharon sin cambios bronquiectáticos permanentes. Sin embargo, no era rado encontrar dilatación bronquial temporal en este grupo, los bronquios regresaban al calibre normal cuando el colapso se volvía a ensanchar—una condición descrita como bronquiectasia reversible.

El tratamiento que se recomienda para el colapso pulmonar incluye inhalaciones de vapor, drenaje postural, y ejercicios de respiración. La broncoscopía inmediata ya no se considera necesaria al menos que se sospeche un cuerpo extraño. No se encontró ninguna diferencia de importancia en la incidencia de la re-expansión del pulmón entre los casos tratados con broncoscopía y los que no se trataron con ella.

Noventa y nueve casos fueron clasificados como bronquiectasia dudosa cuando se vieron al principio. De éstos 47.5% sufrían de asma, una enfermedad frecuentemente difícil a distinguir de la bronquiectasia. Cuarenta de los 99 casos se han desarrollado ahora en verdadera bronquiectasia irreversible después de un período de tres o más años. Fué necesario observar casos de dilatación bronquial dudosa por un período de años, repitiendo los broncogramas a intervalos para determinar las partes permanentemente enfermas.

Great Ormond Street

SYSTEMIC INFECTION WITH SALMONELLA ANATUM

Report of First Case

By CHIEH SUNG, M.D., D.P.H., J. FOURNIER, M.D.,
AND SIANG-YUEN CHANG, M.D.
Shanghai, China

SALMONELLA ANATUM has been recognized as one of the causative organisms for gastroenteritis, especially in the young age group.[1-3] Recently, the authors encountered an infant suffering from diarrhea and a remittent type of fever from whose blood the organism Salmonella anatum was recovered. This is the first proved case of a systemic infection with this organism. The purpose of this report is to present the case history and results of the bacteriologic and serologic studies on the isolated organism.

CASE REPORT

A female infant 1 yr. of age was admitted to the hospital with the chief complaints of fever and diarrhea of 1 wk.'s duration. Stools were watery in character and there were 7 to 8 bowel movements daily. Onset of the fever was said to have been gradual and the elevation of temperature had been high for 2 days only prior to admission. Fever was apparently of the remittent type, rising to a higher level toward the afternoon. Urination became scanty. Appetite was fair. Infant had not appeared too sick at home. Past history and family history were noncontributory.

On admission, patient was markedly underdeveloped and undernourished, weighing 4.2 kg. She appeared pale, but not acutely ill. There was no skin eruption. Cervical, axillary and inguinal lymph nodes were barely palpable. Anterior fontanel was closed with membranous cartilage. Lips were dry and tongue coated. There were no teeth. Throat was slightly infected. Occasional moist rales were heard over the lower part of the back of the chest. Abdomen was slightly distended. Spleen could not be felt and liver was just palpable. She was alert and there were no unusual neurologic signs. Temperature was 39.9°C.

Laboratory findings: Blood—RBC, 2.68 million/cmm.; Hgb., 7.0 gm./100 cc.; WBC, 7.6 thousand/cmm.; polymorphonuclears 65%, lymphocytes 35%. Blood culture taken 8 days after the onset of illness gave a growth of Salmonella anatum. Widal test of the blood taken was negative, O and H antigens of S. typhi, S. paratyphi A, S. paratyphi B, and S paratyphi C being used as the antigens. Urine: yellow and cloudy, acid, albumin 2+, numerous pus cells on microscopic examination. Urine culture was positive for Escherichia coli 4 days after the start of sulfonamide therapy. Stool: yellow and soft, no blood or mucus. Culture of stool after 8 days was positive for Salmonella anatum.

Mantoux tests were negative up to the strength of P.P.D. 25 mg. Roentgenogram of the chest showed no pathologic findings.

Hospital course: Immediately after admission, sulfadiazine and sulfathiazole at 0.12 gm. each and sodium bicarbonate 0.2 gm. q. 4 h. for the 1st 5 days was started. The next 8 days, sulfathiazole 0.2 gm. with sodium bicarbonate q. 4 h. was given; and for the last 2 days of treatment, the dosage was reduced to sulfathiazole 0.2 gm. with sodium bicarbonate q. 6 h. Penicillin was given at 20,000 u. q. 3 h. intramuscularly for 4 days. Liquid diet was offered, and vitamin B complex and vitamin C and calcium gluconate were prescribed. Three subcutaneous infusions with glucose 3% in normal saline were given.

Diarrhea stopped soon after admission. For the 1st 5 days in the hospital, temperature fluctuated mostly between 38° to 40°C. (Fig. 1). On the 6th day, temperature fell rather sharply to normal and thereafter the baby remained afebrile. Urinary findings showed steady improvement; the specimen taken on the 14th day showed no albumin, and only occasional pus cells were seen in the sediment,

From the Shanghai Public Hospital for Children and the Pasteur Institute, Shanghai, China.
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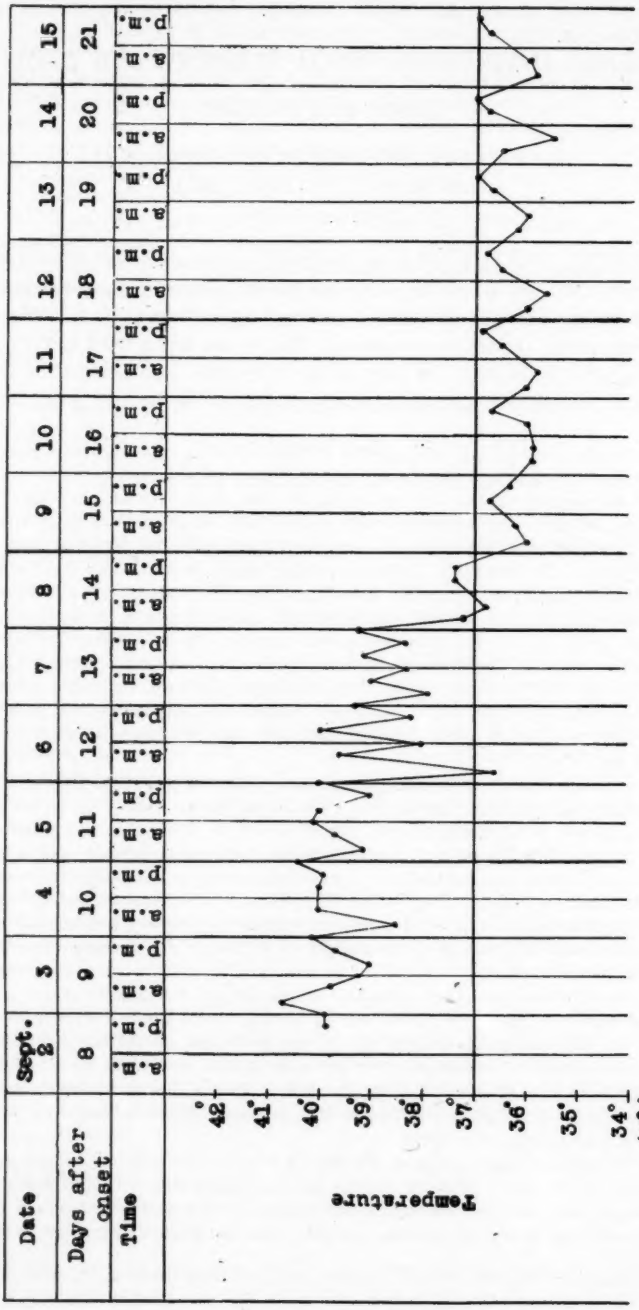

FIG. 1. Temperature chart

but its culture still gave the growth of Escherichia coli. WBC count on the 12th day was 7.7 thousand/cmm. with a differential count of polymorphonuclears 60% and lymphocytes 40%.

One wk. after the positive blood culture, another blood specimen was taken for culture and was subsequently found to be sterile. Agglutination test done on the 9th day with the serum of the patient and the organism isolated from her own blood gave a titer up to the serum dilution of 1/600.

Infant was discharged on the 23rd day, having been afebrile for 17 days in the hospital. Urinary findings were entirely negative. Her general condition was good.

Identification of Organism Isolated from Patient's Blood

Preliminary identification of this gm.-negative motile bacterium isolated from the blood of the patient as a member of the genus Salmonella Lignières was based on the biochemical characteristics as specified by the Salmonella Subcommittee of the Nomenclature Committee of the International Society of Microbiology.[4] The nature of its O antigen was first studied by means of agglutination tests using the slide technic. The organism was found to be strongly agglutinated with the O-sera containing the agglutinin No. III, sera london, newington, and senftenberg having been used in these tests. No agglutination was observed with the other types of O-sera. This fitted the organism into Group E in the Kauffmann-White schema.[5] Subsequently, this organism was agglutinated by O-sera, indicating the presence of the antigens Nos. X and XXVI in its O complex. The presence of these 3 components, III, X, and XXVI, in the O antigen showed that the organism under study belonged to the first subgroup of Group E. To date, this subgroup is known to consist of 14 different types which differ serologically from one another in their H antigen structures.

In order to determine the components of its H antigen in both of its specific and nonspecific phases, further agglutination tests were performed in the test tubes with the organism against the following 13 types of immune sera: S. typhi (with d), S. eastbourne spec. (with e, h), S. thompson spec. (with k), S. london spec. (with 1, v), S. dar-es-salaam-a (with 1, w), S. virchow spec. (with r), S. bareilly spec. (with y), S. kentucky-β (with z^6), S. glostrup-a (with z^{10}), S. paratyphi B nonspec. (with 1, 2..), S. thompson-berlin (with 1, 5..), S. anatum nonspec. (with 1, 6..), and S. gaminara nonspec. (with 1, 7..). A formalinized broth culture of the organism was used with each of these sera in dilutions ranging from 1/100 to 1/6,400. Readings were taken after incubation for 2 hrs. in a water bath at 52°C. Agglutination at the highest titers was noted in the tubes with sera S. eastbourne spec. (with e, h) and S. anatum nonspec. (with 1, 6..). By using the colonies developing on a thick agar plate and again the slide agglutination method, it was found that organisms from some of the colonies were agglutinated only with the agglutinins e and h, while those from the others only with the agglutinins 1 and 6. . This led to the epitomized formula for this organism "III, X, XXVI; e, h ⇄ 1, 6 . . ," which serologically represents Salmonella anatum.

Discussion

The symptomatology in this case simulates that of a paratyphoid-like fever in children. The onset was gradual, and the infant never appeared seriously sick throughout the course of her illness. Diarrhea ceased in about one week, and the whole febrile course lasted for about two weeks. There was evidence of a mild bronchitis. The effect of the sulfonamides or penicillin on the whole course of illness in this patient cannot be evaluated, although the concurrent infection of the urinary tract, culturally proved to be due to Escherichia coli, seemed to have responded favorably to the therapy. She had apparently normal white blood cell counts and differential counts, rather characteristic of the so-called sporadic cases of Salmonella infection.

Numerous case reports of systemic Salmonella infections in man have come from this part of the world.[3, 6–19] According to the classification of these organisms based upon their antigenic structures as outlined in the Kauffmann-White schema,[5] they fall mostly into the following groups: Group A (S. paratyphi A), Group B (S. paratyphi B and S. typhi-murium), Group C (S. blegdam and S. enteritidis). (S. typhi of Group D, more popularly known as Bacillus typhosus, is not included in the present discussion.) Recently,

Salmonella anatum of Group E has been repeatedly isolated from the stools of human beings suffering from gastroenteritis, especially in the young age group[1-3, 15, 20-22] but, as far as is known, never from the blood. At the time when the blood was drawn from this patient for culture, her stools were carrying the organism. To be skeptical, the possibility of fecal contamination of the blood specimen might be considered. However, an agglutination titer of 1/600 is significantly high, and may definitely denote a previous or existing septicemia with the organism, if we take into consideration the facts that agglutinins are usually poorly developed in small infants, and, as a rule, a Salmonella infection limited to the gastrointestinal tract does not produce a high titer of agglutinins in the blood of the patient.

Salmonella anatum Rettger and Scoville,[23, 24] perhaps identical with Salmonella anatis Cornil and Coupet,[25] is recognized to be responsible for a certain epidemic intestinal disorder among ducklings known as keel. Occasionally, the organism may be recovered from the eggs of the duck, although no case of human Salmonella anatum infection has ever been reported in relation to the consumption of meat or eggs of the ducks. Salmonella anatum has been recovered from the intestinal contents of a wild rat in Shanghai.[20] This last finding suggests that rodents may play a role in the spread of this infection.

Summary

A case of Salmonella anatum septicemia in an infant is presented. It is believed that this is the first recorded instance of this systemic infection in man.

The clinical features, laboratory studies on the isolated organism, and the available epidemiologic data on the organism, Salmonella anatum, are discussed briefly.

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SPANISH ABSTRACT

Infección Orgánica General con Salmonella Anatum; Relato del Primer Caso

La Salmonella anatum ha sido reconocida como uno de los organismos que causa gastroenteritis, especialmente en el grupo de poca edad. Este es un relato del caso de un niño que pedecía de diarrea y de un tipo remitente de fiebre, de cuya sangre se sacó el organismo. Es el primer caso probado de una infección sistémica con este organismo.

Este papel trata de las características clínicas, los estudios de laboratoria sobre el organismo aislado y la información epidemiológica que hay sobre el organismo, Salmonella anatum.

11 Hsiang Shan Road

Pediatrics

VOLUME 4 AUGUST 1949 NUMBER 2

SPECIAL SECTIONS

TRENDS

IN HEALTH LEGISLATION AND ADMINISTRATION

By JOHN P. HUBBARD, M.D., *Contributing Editor*

This and subsequent descriptions of events and trends are intended to be unbiased and factual, presenting both sides of controversial matters so that conclusions may be formed from critical appraisal of things as they are. These statements do not necessarily reflect the opinion of the writer nor are they to be interpreted as official opinion of the Academy.

AMONG the significant trends observable throughout the United States today are the many positive steps being taken to promote child health. At regional, state and local levels, recommendations are being made and carried through which naturally and appropriately vary from area to area. Much of this action is directly attributable to the reports of the Academy's study appearing in increasing number for the individual states. As of present date, 11 states have published their reports, and all but a few of the others are in varying stages of preparation. Henceforth, it will be a function of this column to review important trends in pediatrics at state and local, as well as national, levels.

Readers of this column are invited to offer contributions describing trends with which they may be particularly familiar in their own areas. Such contributions should be limited to factual reporting of events or plans. This is not the place for controversial material.

* * *

It is highly appropriate that North Carolina, the pilot state for the Academy's study, should be among the first to take active steps to remedy some of the gaps revealed by the study. The following are excerpts from a mimeographed release dated March 1, 1949, under the title, "Premature Infant Care Program," North Carolina State Board of Health, Division of Maternal and Child Health, Raleigh, N.C.

Need for Program for Premature Infant Care

"In the survey of the American Academy of Pediatrics Study of Child Health Services in North Carolina in 1945, the infant death rate in North Carolina was one of the highest in the nation. There were only seven states in 1945 that had a higher infant

death rate than North Carolina. Since one third of infant mortality (infants under one year) and one half of neonatal mortality (infants under one month) are attributable to prematurity, if we are to lower the infant death rate, then there is no better place to start than on a program for the care of prematurely born infants.

"Emphasis has been placed on good health in North Carolina in recent years and there has been established the Medical Care Commission. The North Carolina State Board of Health, as usual, is taking its place as a first line of defense in the health problems of the State. The Department of Maternal and Child Health under the directorship of Dr. George M. Cooper has recently instituted a premature infant care program with the aid of the U.S. Children's Bureau funds and the encouragement of the North Carolina Pediatric Society.

"In 1947, there were 111,282 reported live births in North Carolina. Of these live births, 3,920 died under one year of age. Of these infant deaths, 1,364 or 34% were reported as caused by prematurity. From a statistical survey of thousands of premature infant deaths in several states, it has been found that 90% of the prematures who die, die within the first 48 hours. It is estimated by various authorities that between 40 and 50% of these deaths could be prevented if adequate physical and professional care were provided during this critical period. It is part of the purpose of this premature infant care program to give adequate physical and professional care to the infants in time. Our local health departments and nurses are to be alerted to the professional possibilities of this premature infant care program.

"Recently there has been introduced in the 1949 General Assembly a bill for the reporting of infants prematurely born in the State of North Carolina. This bill has been passed and a copy of this is being attached to this draft.

Principles

"The following is a statement of the purpose of the program for premature infant care:

"1. To give assistance when possible to every premature infant in the State where the family is not able to carry the financial burden of this expense.

"2. To improve the care of the premature infant by lending assistance only where at least minimum standards are provided in the physical setup for care of prematures and only when professional care is adequate.

"3. To encourage hospitals and professional men throughout the State to meet these requirements.

"4. To enlist the aid of local health departments and their nurses to participate in this program.

"Through the above principles and the cooperation of the medical profession, U.S. Children's Bureau, North Carolina Pediatric Society, participating hospitals, State and local health departments, we hope that a diminution in premature infant morbidity and mortality in North Carolina will be obtained and thus a decrease in the infant death rate. . . .

Qualifications

"The minimum standards required of the hospital care:

1. Nursery for well premature infants born in the hospital.
2. Isolation nursery.
3. Separate facilities for premature infants born outside of the hospital.
4. Oxygen available in the nursery.

5. Suitable incubators (preference, Gordon Armstrong or similar model).

6. There should be in charge of the Premature Infant Unit a graduate nurse throughout the 24 hour period, who has had a period of experience and instruction in the care of premature infants which meets the requirements set up by the State Board of Health.

7. Adequate isolation technique.

8. Air conditioning (optional).

9. A. *Medical Care*—There should be a pediatrician in charge of the premature nursery who is certified by the American Board of Pediatrics or eligible for certification and who is a member of the staff of the hospital and who meets the approval of the State Board of Health, Division of Maternal and Child Health. It should be his responsibility to establish medical procedures.

Nursing Care—There should be such a nurse-patient ratio at all times to assure adequate care of the premature infants of all degrees of prematurity. The first 48 hours of the infant's life in the hospital being the critical period, there should be a nurse in constant attendance with the infant during this period.

B. *Equipment*—Furnishings, equipment, size and construction should compare favorably with Standards and Recommendations for Hospital Care of Newborn Infants of the American Academy of Pediatrics Committee on Fetus and Newborn (copies of which may be obtained from the North Carolina State Board of Health Division of Maternal and Child Health). . . .

Pediatricians

"*Qualifications*—Certification or eligibility for certification by the American Board of Pediatrics is desirable; however, the program is also open to those physicians who restrict their practice to pediatrics and have had at least one year of pediatric internship in a hospital approved for pediatric training, and have had two years of pediatric practice. The pediatrician must of course be a member of the staff of the hospital selected to care for the baby.

"*Remuneration*—Pediatricians are to be paid on individual case basis, the rate to be $3.00 per day, regardless of the number of visits required, the minimum of one visit a day, for the first week, then $2.00 a day for succeeding days' stay, up to a maximum of $50.00, regardless of how much longer thereafter the child may be confined in the hospital. That is, the total maximum cost for each case shall not exceed $50.00. The pediatrician will agree on his statement of services to accept payment in full from the health department. . . .

"An Advisory Committee of three physicians has been appointed by the State Board of Health to advise on policies of the Premature Infant Care Program. These physicians have worked with the Maternal and Child Health Department of the State Board of Health in development of this program. The physicians are: Dr. Arthur H. London, Durham, who is Regional Chairman of the American Academy of Pediatrics; Dr. Charles R. Bugg of Raleigh, who is State Chairman of the American Academy of Pediatrics; and Dr. Angus McBryde, Pediatric Department, Duke Hospital, Durham, who is in charge of the Premature Infant Center at Duke Hospital.

"This draft is subject to further revision as this program gets underway."

GEORGE M. COOPER, M.D., *Director*
Division of Maternal and Child Health

ROBERT J. MURPHY, JR., M.D.
Pediatric Consultant

PUBLIC HEALTH, NURSING AND MEDICAL SOCIAL WORK

LEONA BAUMGARTNER, M.D., *Contributing Editor*

THE DOCTOR AND SOCIAL WORK

PHYSICIANS sometimes have difficulty in understanding why social workers are turning up in so many places, what social workers do, and how physicians can use their services. In the old days the family doctor knew all about the social problems of his families, as well as their physical ailments. This is not as true today. Social work as a discipline is a relatively new field, though helping the poor and the infirm is an ancient art.

Moreover, family living in this generation is different from what it was in the last. The absence of older children and maiden aunts, the migratory nature of modern life, the lack of space for urban families, the break-up of many homes, these and many other problems have tended to complicate the rearing of children. Families probably need more outside help than they did a generation ago. Moreover, modern psychosomatic medicine is acquiring a new concept of what the doctor's role is. It, therefore, seems fitting for physicians of today to know more of social work. There are many specialists in that field. There is the child welfare worker, the medical social worker, the psychiatric social worker, the family case worker, the group worker and the school social worker. From all of these, the physician may receive some help in solving the problems of his patients. The article "Social Adjustment of Six Patients with Hemophilia Prior to and During Prophylactic Treatment" (PEDIATRICS 3:588, 1949) was a description of the way in which medical social workers help physicians who are treating hemophilia. The contribution printed in this column on medical social work by Miss Soule attempts to round out that picture and to describe some of the background of medical social work. It is hoped that contributions on other aspects of social work will follow.

THE DOCTOR AND THE MEDICAL SOCIAL WORKER

By THEODATE H. SOULE

Two books have been published recently which should add both to medical and lay understanding of medical social work. One is "Widening Horizons in Medical Education,"[1] a report of a joint committee of the Association of American Medical Colleges and the American Association of Medical Social Workers to study the teaching of social and environmental factors in medicine; the other is "The Rehabilitation of the Patient" by Caroline H. Elledge which describes the contribution of medical social work to the rehabilitation of handicapped persons.[2] The first is concerned primarily with the concepts the medical student should know and the teaching projects in use in various medical schools, but there is a chapter on the function of the medical social worker and what she adds toward understanding the patient and helping him meet the social and emotional

Miss Soule is Director of Social Work at New York Hospital, New York, N.Y., and Past President of the American Social Workers Association.

problems connected with his illness. Mrs. Elledge's book gives detailed case material which shows graphically how illness and disability complicate human relationships and influence spiritual as well as physical growth and development. In his foreword to "The Rehabilitation of the Patient," Dr. Philip D. Wilson gives the following description which is applicable to all medical social workers, not only to those serving handicapped persons exclusively: "No one is better fitted to make the early approach to the patient, to win his confidence and investigate the family and social background, than is the medical social worker. And then, with an understanding of the problems that confront the patient and with her knowledge of the community resources which may be used to assist the patient and the advice and help of the physicians who are directing the treatment, she should be able to steer the individual in a direction which will make him both a social and economic asset to his community." And it should be added that aid and support are offered, not only in regard to environmental difficulties, but also in respect to the sources of misunderstanding and tension which may contribute to the degree or duration of the patient's disability.

The first case history in Mrs. Elledge's book shows the complex nature of medical social problems and the fact that how the patient may feel about his illness or disability is as important as what treatment is planned. Attitudes and feelings frequently affect results of treatment to an astonishing degree. John was a fatherless 14 year old boy whose leg had to be amputated above the knee due to a malignant tumor of the bone. Overhearing what operation was planned, he contemplated running away from the hospital. The social worker recognized his panic over the anticipated pain and the fear that he would never be able to go to school again, to play with other boys or to do anything to contribute to his mother's earnings. As he said with unconscious pathos, "I am only 14 years old and can't get along without my leg." Interpretation of these feelings to the doctor led, not to glossing over the fears, but to help in considering them from all angles. The doctor and the worker, together with John and his mother, made plans which eventually led to his return to everyday living with confidence and with hope for a satisfying future.

The exercise of teamwork is characteristic of modern medical practice. The doctor assumes leadership and the other professional personnel in the medical or health organizations work with him. The special contribution of the medical social worker lies in the relating of medical and social factors and in the treatment of particular social problems connected with the care of individual patients. Knowledge regarding health and disease, scientific medicine and medical practice; the acceptance of the concept of the organism as a whole; understanding of the role of emotions and the meaning of behavior in illness, and the knowledge of community resources and how to use them most effectively are all a part of the education of the medical social worker.

The present course of training in medical social work developed under the leadership of the American Association of Medical Social Workers which was organized in 1918. A standing committee on education was established and following the first comprehensive study of medical social work practice which was made under the auspices of the American Hospital Association, the American Association of Medical Social Workers in 1923 advocated a two year postgraduate curriculum as the desirable professional foundation. Such a two year program leading to a Master's Degree must offer a basic social work curriculum approved by the American Association of Schools of Social Work

and additional related classroom and field work courses in medical social work. This educational foundation has been accepted by the American Association of Medical Social Workers as the basis for practice in medical social work and eligibility for membership in the professional organizations. At present there are 22 graduate schools of social work with accredited medical social work courses; a list of these schools appears at the end of this article.

Although medical social work was first practiced in hospitals and clinics and the largest number of positions are still in these organizations, the acceptance of its contribution as an integral part of medical care opened the way for its use in noninstitutional health and medical care programs. Experienced medical social workers are now employed in local and State departments of health and welfare and in rehabilitation agencies chiefly as consultants but also as practitioners. At the Federal level, medical social consultants are part of the programs administered by the Federal Security Agency, the crippled children's and maternal and child health services of the Children's Bureau, those of the Bureau of Public Assistance and in the Divisions of Tuberculosis and Hospitals of the Public Health Service. Medical social workers are also employed in specialized voluntary agencies for the prevention of blindness and the care of patients with infantile paralysis, cancer, heart disease, tuberculosis and other chronic conditions. The demand for adequately trained workers greatly exceeds the supply. Insufficient opportunities for field practice under good supervision in hospitals, which limit the number of students accepted by schools of social work, and the cost of training and low salary scale as compared with social workers outside of medical and health organizations are obstacles to recruitment for the profession. Some scholarship aid has been available through a few organizations, the most extensive program being that of the National Foundation for Infantile Paralysis.

References

1. Curran, Jean A., M.D., and Cockerill, Eleanor, Widening Horizons in Medical Education, Association of American Medical Colleges and American Association of Medical Social Workers, New York, The Commonwealth Fund, 1948.
2. Elledge, Caroline H., Rehabilitation of Patient, Philadelphia, J. B. Lippincott Company, 1948.

List of Graduate Schools of Social Work with Accredited Medical Social Work Courses

Boston College
School of Social Work
126 Newbury St.
Boston, Mass.

Boston University
School of Social Work
84 Exeter St.
Boston, Mass.

Bryn Mawr College
Graduate Department of Social Economy and Social Research
Bryn Mawr, Pa.

Catholic University of America
The National Catholic School of Social Service
Washington, D.C.

Fordham University
Graduate School of Social Work
134 E. 39th St.
New York, N.Y.

Howard University
Graduate School of Social Work
Washington, D.C.

Indiana University
Division of Social Service
122 E. Michigan St.
Indianapolis 4, Ind.

McGill University
Montreal School of Social Work
3600 University St.
Montreal, Canada

Nashville School of Social Work
Nashville, Tenn.

The New York School of Social Work of Columbia University
122 E. 22nd St.
New York, N.Y.

St. Louis University
School of Social Service
St. Louis, Mo.

Simmons College
School of Social Work
51 Commonwealth Ave.
Boston 16, Mass.

Tulane University
School of Social Work
New Orleans, La.

University of California
Graduate School of Social Welfare
Berkeley, Calif.

University of Chicago
School of Social Service Administration
Chicago, Ill.

University of Louisville
Raymond Kent School of Social Work
Louisville, Ky.

University of Minnesota
School of Social Work
Minneapolis, Minn.

University of Pittsburgh
School of Social Work
Pittsburgh, Pa.

University of Southern California
Graduate School of Social Work
Los Angeles, Calif.

Washington University
George Warren Brown School of Social Work
St. Louis, Mo.

Western Reserve University
School of Applied Social Sciences
Cleveland, Ohio

University of Washington
Graduate School of Social Work
Seattle, Wash.

INTERNATIONAL NEWS AND REPORTS

THE SIXTH INTERNATIONAL PEDIATRIC CONGRESS, ZURICH, SWITZERLAND, 1950

FIRST COMMUNICATION

During the Fifth International Pediatric Congress in New York a Committee of Seven (composed of Professors R. Debre, Paris; Gomez Santos, Mexico; H. F. Helmholz, Rochester, Minnesota, former President; L. Emmett Holt, Jr., New York, Secretary-General; Maslow, Leningrad; A. Moncrieff, London, and G. Fanconi, Zurich, who was elected President of the 6th International Pediatric Congress) met in order to draw up Rules for the Constitution of an International Pediatric Association (I.P.A.).

Pending the acceptance by the International Congress of 1950, this Committee of Seven decided the following:

1. To establish a list of the various national Pediatric Societies as well as of their presidents and possibly their members. The undersigned, as well as Dr. L. Emmett Holt, Jr. (Bellevue Hospital, 26th Street and First Avenue, New York 16, N.Y.), ask you kindly to send them the required information.
2. To create an International Reference Journal of Pediatrics.
3. To give advice to other organizations concerned with child health and welfare.
4. To organize international regional meetings in order to discuss special problems of immediate importance.

Until the coming Congress in 1950 the official communication of the I.P.A. will be published in six languages in the regular numbers of Helvetica Paediatrica Acta. These will be sent free of charge to the Presidents of the National Societies.

The undersigned requests that the various National Pediatric Societies kindly communicate to him, as soon as possible, suggestions for the main subjects to be discussed at the 6th International Pediatric Congress.

President of the 6th International Pediatric Congress, 1950
G. FANCONI

SECOND COMMUNICATION

It has been decided to hold the Congress during the last 10 days of July, 1950. The actual Congress will last 4 to 5 days. It is proposed to hold 2 plenary sessions, each lasting half a day, and a series of simultaneous group sessions. Themes for the group sessions have been drawn up based on suggestions from all over the world. Each group session will consist of pre-arranged lectures lasting from 10 to 30 minutes, followed by an open discussion in which no contribution may exceed 5 minutes. Notifications for important lectures not included in the program can only be accepted through the secretariats of the various national pediatric societies.

The manuscripts of lectures (without illustrations) must reach the Organizing Committee not later than April 1, 1950, in order to permit their printing and distribution to conference members in advance.

It is planned to hold a scientific exhibition lasting 2 weeks in a hall adjoining the Conference rooms to display the lecturers' graphs, photographs and other illustrations. The Organizing Committee will provide the exhibition space and cellotex sheets necessary to hang the graphs free of charge. Show cases for lantern-slides, colored photographs, etc., can only be provided if ordered and paid for well in advance. All those invited to lecture can display their material; other conference members must secure special permission from their national pediatric societies beforehand.

Following the first notice in May 1948, only 24 nations have notified the Secretary-General, Dr. L. Emmett Holt, Jr. (Bellevue Hospital, 26th St. and First Avenue, New York 16, N.Y.) and the President of the Congress, Prof. G. Fanconi (Kinderspital, Zurich) of the names of the president and other officers of their national pediatric societies. These will receive free of charge, until the Congress in 1950, copies of "Helvetica Paediatrica Acta" with the official notices of the I.O.P. in 6 languages.

THIRD COMMUNICATION

The 6th International Congress of Pediatrics in Zurich will be held from July 24 to July 28, 1950, and from July 21 to July 31 the scientific exhibition, in which the World Health Organization will also take part. The languages admitted at the Conference are English, French, German, Italian, Russian and Spanish, but mutual understanding would be greatly facilitated by the use, as far as possible, of English or French. In the volume containing the lectures, contributions in English, French, German and Italian will be printed in the original languages. For technical and financial reasons it is not possible to publish the lectures given in Russian and Spanish; we request, therefore, the respective authors to enclose a translation in either English or French.

The exhibition guide and the conference program will be printed in English and French.

The President: PROF. G. FANCONI
The Secretary-General: DR. H. ZELLWEGER

SPECIAL NOTICES

Two plenary sessions lasting half a day each will be held on July 24 and 28, 1950, as well as numerous simultaneous section meetings. Ten minutes are allowed for each contribution in the section meetings, with the exception of a few major contributions arranged by the Organizing Committee lasting 20 to 30 minutes.

For the scientific exhibition, we propose to provide boxes about 6½ ft. deep, 6½ ft. wide and 5 ft. high, that is, about 100 sq. ft., exhibition space. Each box will contain an electric light plug for the setting up of microscopes and similar equipment. Each exhibitor is requested to indicate in his application how much space he requires and whether he desires a microscope, etc. A small number of illuminated show cases for lantern slides of 2 x 2 in. and 3.6 x 4.8 in. can be procured for exhibitors who pay the cost price in advance.

The number of show boxes is limited. If the number of applications for exhibition space is too large, the Organizing Committee will make a selection. As a general rule only new findings since 1947 can be exhibited.

Film shows: Films cannot be shown in the section meetings, but special rooms will be provided for didactic and scientific film shows. If possible, only 16 mm. films should be presented. Film demonstrators should state in their application the length, title and, in a few brief sentences, the contents of the film.

Demonstrations of apparatus, special experiments, etc., should, in the demonstrator's own interest, be announced as soon as possible, so that the necessary room and other arrangements can be provided.

Closing date for applications: The Organizing Committee should be informed as soon as possible about lectures, exhibits and demonstrations. Closing date: January 15, 1950.

Publications: Before the beginning of the Conference all lectures will be pubished in a lecture volume. This will be given free of charge to each member holding a Conference ticket. One page (45 lines of 60 letters each) will be provided for a lecture lasting 10 minutes and for longer lectures an additional page for every 10 more minutes.

A printed guide to the exhibits will be issued, in which each exhibitor will have at his disposal half a page (20 lines of 60 letters) for a brief description of his exhibit in either English or French. Contributions to the lecture volume and exhibition guide which exceed the permitted length will be shortened by the Conference Secretary, who can take no responsibility for these modifications. Contributions received later than April 1, 1950, cannot be taken into consideration.

The Organizing Committee of the 6th International Congress of Pediatrics 1950 in Zurich has appointed the American Express Company, Inc., and its branch offices as official travel agency for this Conference.

The American Express Co. in collaboration with the authorities concerned will arrange for accommodation in Zurich and for the travel arrangements of the delegates from the various countries. Details will be published in a prospectus issued by the American Express Company with the help of the Organizing Committee.

DRAFT PROGRAM FOR THE GROUP LECTURE

FIRST SECTION. *Professional Problems and Social Medicine.*

1. Professional Problems.
   a) The Teaching of Pediatrics before and after Graduation; the Pediatrician as General Practitioner or Consultant.
   b) The Effect of Socialization on Pediatrics.
2. Social Medicine.
   a) The Prevention of Epidemics by Active Immunization.
   b) Problems of the Protection of Children in Countries with a High and in Countries with a Low Child Mortality Rate.
   c) Perinatal Mortality and its Prevention with Special Attention to Diet (Human Milk-Animal Milk).
   d) The Effect of Undernourishment, Illness and Bad Social Conditions during Pregnancy on Infantile Mortality and Morbidity in the First Year of Life.
   e) Care and Feeding of Premature Infants.
   f) Caries of the Teeth and its Prophylaxis by Application of Fluorine, etc.

SECOND SECTION. *Pathology of the Newborn.*

1. Embryopathies and Congenital Malformations.
2. Rhesus, A-B-O and other Incompatibilities (Icterus gravis et simplex neonatorum).
3. Disturbances in the Adaptation of the Metabolism.
4. Hemorrhage of the Newborn.

THIRD SECTION. *Problems of Growth.*

1. Scientific Observation of the Growth and Development of the Normal Child.
2. Secondary Sex Characteristics and the Endocrine Glands.
3. Pubertas Præcox.

FOURTH SECTION. *Basic Research.*

Advances in Medicine as a Result of the Use of Isotopes.

FIFTH SECTION. *Metabolic Disorders.*

1. Disturbances of the Amino Acid Metabolism
2. Treatment of Diabetes Mellitus with Special Attention to Later Complications.

SIXTH SECTION. *Blood Diseases.*

1. Treatment of Leukemia and Malignant Tumors.
2. Hemolytic Diseases of the Older Child.

SEVENTH SECTION. *Etiology of the Diarrheal Diseases and Dystrophies.*

1. Constitutional Forms.
2. Infectious Forms.
3. Forms caused by Malnutrition and Undernourishment.

EIGHTH SECTION. *Virus Diseases.*

1. The Set-up and Value of the Virus Laboratory.
2. Neurotropic Virus Diseases.
3. Virus Pneumonia.
4. Virus Diarrhea.

NINTH SECTION. *Bacterial and Protozoal Diseases.*

1. Treatment of Congenital Syphilis with Special Attention to Penicillin.
2. The Use of Streptomycin in Disease other than Tuberculosis.
3. Aureomycin, Chloromycetin and other new Antibiotics.
4. Histoplasmosis and Toxoplasmosis.

5. Tropical Diseases:
   a) Treatment of Malaria.
   b) Leishmaniosis of Skin and Internal Organs.
   c) Kala Azar.

TENTH SECTION. *Surgery in Childhood.*

1. Heart Surgery.
   a) Progress in the Diagnosis of Congenital Heart Disease.
   b) Heart Operations.
2. Other Surgery of the Thorax.
   a) Treatment of Bronchiectasis.
   b) Surgical Treatment of Malformations of the Esophagus.
3. Brain Surgery in Childhood.
   a) Pachymeningosis.
   b) Hydrocephalus.
   c) Epilepsy.

ELEVENTH SECTION. *Psychiatry and Neurology.*

1. Child Psychiatry and Neurology.
   a) Psychic Changes due to Encephalitis.
   b) Psychic Changes due to Multiple Aberrations.
   c) Organic Forms of Dementia, e.g., Dementia Infantilis Heller.
   d) Psychic and Neurologic Damage following the Use of Medicaments (Mercury, Streptomycin, Atabrine, etc.).
   e) Problems of the Resocialization of Neurologically Damaged Children.
      aa) Organic Rehabilitation.
      bb) Psychologic and Psychiatric Rehabilitation.
   f) Pedagogic Problems in the Children's Hospital.
2. The Importance of the Electroencephalogram in the Differential Diagnosis:
   a) of Convulsive Diseases.
   b) of Psychologic and Behavior Disturbances.

TWELFTH SECTION. *Miscellaneous.*

Treatment with Maximal Doses of Vitamin D and Ill Effects of Vitamin D, etc.

NEWS AND ANNOUNCEMENTS

Chicago Pediatric Society

Announcement has been made of the winners of the Residents' Competition held by the Chicago Pediatric Society in Chicago, Ill., on May 17, 1949.

Tied for first prize: Dr. W. Robert Elghammer, Children's Memorial Hospital, and Dr. Albert M. Hand, Children's Memorial Hospital.

Third Prize: Dr. Julian D. Levinson, Cook County Hospital.

Fourth Prize: Dr. David M. Jordan, Michael Reese Hospital.

Fifth Prize: Dr. Jack W. Singleton, University of Illinois.

* * *

New Members of the Society for Pediatric Research

The following new members have been elected to the Society: Neva M. Abelson, Philadelphia; Arthur W. Chung, New York; Andrew Lawrence Chute, Toronto; Joseph Dancis, Flushing, N.Y.; Gilbert B. Forbes, St. Louis; Kendrick W. Hare, Buffalo; James Gilliam Hughes, Memphis; John D. Keith, Toronto; Weston Maynard Kelsey, Winston-Salem, N.C.; Jack Metcoff, Boston; Rosa Lee Nemir, Brooklyn, and Henry K. Silver, San Francisco.

ADDENDUM

Mitchell, N., et al., Congenital hemolytic disease resulting from A-O isoimmunization, Pediatrics 3:813, 1949.

The mother in Case 2 has been delivered of another child just a few weeks ago. The infant was born with jaundice and on the second day of life an exchange transfusion was carried out with apparently good results. The infant is at present alive and healthy.

Line 21 on page 818 should read "present three cases" instead of "two fatal cases."

BOOK REVIEWS

HUMAN RELATIONSHIPS IN PUBLIC HEALTH, Geddes Smith, New York, N.Y., Commonwealth Fund, 1948, 15 cents, 18 pp.

This is the title of a small pamphlet just issued by the Commonwealth Fund of New York.* Written by Geddes Smith, an associate of the Fund, it describes an institute on mental health in public health which was held in the summer of 1948. Students at the institute were health officers of California counties and cities, or bureau chiefs in the State Health Department, with representatives of public health services of Tennessee, Mississippi, and Oklahoma. Eight psychiatrists, 3 pediatricians with psychiatric training, and 5 public health leaders took responsibility for focusing discussions. Mr. Smith, in this 18 page pamphlet, has described what went on in the 2 weeks during which time the group discussed human relations in public health. There is much of interest to pediatricians in this discussion, not only from the point of view of an approach to their own practice, but also to an interesting teaching-method. By and large, the institute followed the pattern previously set down by the Commonwealth Fund in Minnesota when they promoted an institute to teach psychotherapy to the general practitioner. That pattern is a combination of clinical practice and observation, formal presentation of psychiatric points of view in lectures, and abundant opportunity for an informal exchange of ideas. A more lengthy volume reporting the conference will ultimately be available but Mr. Smith concludes, in general, that this is what the group decided:

1. The psychiatric attitude differs significantly from traditional public health attitudes. 2. Mental health is something that intimately affects the health department in all its parts and relationships. 3. Psychiatry offers a specialized therapeutic service which is not readily accessible. 4. The health department can improve the mental health of its community, but the first step is not usually to organize a mental hygiene clinic.

The group also agreed that the single strategic point of attack on which public health efforts should be focused in order to have maximum effect is in the mother-child relationship. They pointed out that the well child conference, though it reaches only a fraction of the population, might well take a place of first importance in the mental hygiene program of the health department. This commentator believes that practicing physicians will find some of the ideas in this pamphlet, in the book that is to appear, and in the volume entitled "Teaching Psychotherapeutic Medicine, An Experimental Course for General Physicians" (edited by Helen L. Witmer, Commonwealth Fund, $3.75) much that will be of interest and of direct help in day to day practice.

PROBLEMS OF EARLY INFANCY, edited by Milton J. E. Senn, M.D., New York, N.Y., Josiah Macy, Jr., Foundation, 1948, $1.00, 120 pp.

Subject matter includes the multiple discipline approach to most of the medical and health problems of this period. Reporting and publication of transactions of such conferences is an important contribution to our knowledge and should be one of the purposes of the conference in order to reach a larger audience than can attend. The editor has done a good job of keeping the text short and clear, especially the discussion.

MODERN TRENDS IN PSYCHOLOGICAL MEDICINE, edited by Noel G. Harris, New York, Paul G. Hoeber, Inc., 1948, $10.00, 439 pp.

This book follows the trend now apparent in having each chapter written by a different author. The multiplicity of authors and diversity of subjects make it a difficult book to review and evaluate. The work covers a broader field of approach to the subject than any yet seen by the reviewer. All of the chapters, excepting three, cover their subject matter well and are written in clear,

* Available from the Commonwealth Fund, 41 East 57 Street, New York, N.Y., in quantity for free distribution by health departments, medical schools, schools of public health and nursing and other health agencies. Single copies 15¢.

concise, understandable language. The titles range from "The Physiology of Emotion" and "Electrophysiology in Psychiatry" through "Psychotherapy" to sociologic studies, such as "Character Formation in Relation to Education" and "Marriage and Family Life."

The editor in the introduction states that his purpose was to "produce a stimulus to thought not only in psychiatrists but also in other members of the medical profession, as well as in educationists and all those dealing with the character formation of children." He has produced a book which should accomplish its purpose in a large measure. It must be admitted, however, that the majority of the chapters are written on a level requiring some knowledge of psychiatric and neurologic literature for their understanding. The book should be interesting and profitable reading for pediatricians who are interested in the over-all picture of child welfare. Three chapters are of such calibre as to deserve individual mention. The chapter on "Physiology of Emotions," by Samson Wright, covers the subject exceedingly well from both the psychologic and physiologic viewpoints and is accompanied by understandable and pertinent charts and sketches. R. G. McInnes has a chapter on "The Causative Factors in Mental Disturbances" which is recommended to all medical men regardless of their specialty. It most clearly states the case for the medical approach to a patient which views man as a total functioning organism rather than the mechanistic approach which only considers segments of his physiologic and psychologic functioning. He also discusses the function of the brain in a highly rational philosophic manner. All facets of causation of mental disturbance, from genetic causes through endocrine and vitamin factors to psychologic factors, are weighed and evaluated in a highly objective manner. "The Principles of Mental Hygiene" by H. V. Dicks is an excellent discussion of this controversial subject and leaves one with a feeling of optimism and hope in regard to the future place of these principles in our culture.

SOME ASPECTS OF HOSTILITY IN YOUNG CHILDREN, Anneliese Friedsam Korner, New York, Grune & Stratton, Inc., 1949, $3.50, 194 pp.

Hostility in children is a personality characteristic which causes great concern to parents, educators and others involved in child-rearing practices. There is much misunderstanding of the hostile and aggressive impulses of children and these characteristics are usually measured in terms of adult feelings. This monograph is the culmination of a study by a psychologist who attempted to scrutinize and examine the feelings of hostility in small children which was directed primarily against parents and parent-substitutes. One of the aims of the investigation was to compare ways in which a group of children of preschool age dealt with their hostility at the level of play and fantasy with the ways in which they were employed in real-life situations. Other questions were also examined; for example, the degree of consistency in which the child expressed hostility under different types of play situations, and the frequency of hostility against members of the family. The subjects consisted of 20 children between the ages of 4 and 6 whose I.Q.s ranged from 90 to 126. The majority were 2nd generation Americans coming from a fairly low socio-economic level; they comprised the entire population of a kindergarten group in a day nursery in New York City.

The experimental procedures included presenting children with incomplete stories which they were asked to complete in word and play, and free-play interviews with each child; in addition, hostility in the home was studied by means of interviews with 1 or both parents. The data were analyzed quantitatively and qualitatively. It was concluded that expression of hostility in play and real life, although varying in degree, was universal in this group of presumably normal preschool children. The sample studied also showed inconsistencies between hostility expressed in play and hostile behavior reported by parents. The children showed 4 patterns with respect to expression of hostility. Knowledge about the parental attitude toward a given child frequently illuminated all of his behavior patterns. Although a causal relationship between hostility expression and parental rejection in individual children was believed to exist, the existence of such a causal relationship could not be substantiated from the numerical evidence in this survey. The sample showed that severe corporal punishment had occurred in children who were reported as strongly hostile in behavior in real-life.

Although the monograph may appear to the average pediatrician to represent literature which is more suitable for an educator or a psychologist, it contains much data of value for anyone who is interested in the personality development and behavior of children.

AN INTRODUCTION TO MEDICAL MYCOLOGY, George M. Lewis, M.D., and Mary F. Hooper, M.D., ed. 3, Chicago, The Year Book Publishers, Inc., 1949, $8.50, 356 pp.

The book is divided into 2 parts: Part I, "Clinical, Theoretical and Experimental Aspects," and Part II, "Laboratory Methods." Part I starts with brief reviews of the history of medical mycology and of the classification, structure and physiology of fungi. There follows a short exposition of methods of diagnosis, and an extensive discussion of immunologic phenomena, particularly in the dermatomycoses. The rest of this section is concerned with an orderly presentation of the clinical aspects of the mycoses, superficial and systemic. The former is excellent, the latter inadequate. In Part II, the technical aspects of the laboratory isolation and identification of pathogenic fungi are discussed, together with the details of such technics as passive transfer tests, skin tests and the use of Wood's light. This part concludes with a lengthy presentation of the characteristics of practically every known pathogenic fungus. It is excessively illustrated, particularly in Part II.

The principal objection to this division into Parts I and II is that discussions of the etiologic agent should go along with the discussion of the clinical picture—not be separated completely and relegated to the back of the book as in this case.

Part II, if not fused in with Part I, as it should be, at any rate could be cut in length by ½ to ⅔, without loss of essential material.

The nomenclature leaves something to be desired; occasionally, it is definitely not in accord with generally accepted names (e.g., Torula Histolytica vs. Cryptococcus neoformans).

Although the dermatomycoses, from the standpoint of frequency, are far more important than the systemic mycoses, the number of words devoted to the former is out of proportion. The treatment extended to the latter is definitely inadequate. This applies not only to the clinical sections, but the laboratory aspects as well. Coccidioidomycosis and histoplasmosis are handled particularly poorly; the chapters on these diseases contain errors of commission as well as omission. It is evident that the authors are not sufficiently familiar with them. Important recent review articles are not given in the bibliography. Other manuals or handbooks of clinical mycology are far superior in this respect and less expensive.

The detailed discussion of immunity in Chapter VI is entirely too long and out of place; furthermore, it revolves almost completely around the interpretation of the trichophytin skin test.

As a text or reference book on medical mycology, this book leaves much to be desired. This is easily detected by a cursory examination of the book.

The format is excellent. The book is easy to handle and has good printing and the reproductions of photographs are especially commendable. The illustrations themselves show precisely what they are meant to show. Much of the discussion, particularly of the superficial fungous infections, is excellent, probably not equalled in other texts.